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- (73) Patenthaver: **Takeda Pharmaceutical Company Limited, 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka
541-0045, Japan**
- (72) Opfinder: **ONO, Koji, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**ITO, Masahiro, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**TANAKA, Toshio, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**ASANO, Moriteru, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**HIRAYAMA, Takaharu, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**FUJIMOTO, Jun, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**SAKAUCHI, Nobuki, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
**HIRATA, Yasuhiro, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0052, Japan**
**TOITA, Akinori, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
Fujisawa-shi, Kanagawa 251-0012, Japan**
MORISHITA, Nao, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,

Fortsættes ...

Fujisawa-shi, Kanagawa 251-0012, Japan
 KOKUBO, Hironori, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
 Fujisawa-shi, Kanagawa 251-0052, Japan
 IMAEDA, Yasuhiro, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
 Fujisawa-shi, Kanagawa 251-0012, Japan
 MAEZAKI, Hironobu, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
 Fujisawa-shi, Kanagawa 251-0012, Japan
 CARY, Douglas Robert, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
 Fujisawa-shi, Kanagawa 251-0012, Japan
 MIZOJIRI, Ryo, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome,
 Fujisawa-shi, Kanagawa 251-0012, Japan
 CHO, Nobuo, c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-
 shi, Kanagawa 251-0012, Japan
 BANNO, Hiroshi, c/o Axcelead Drug Discovery Partners, Inc., 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi,
 Kanagawa 251-0012, Japan
 TOKUHARA, Hidekazu, c/o Axcelead Drug Discovery Partners, Inc., 26-1, Muraoka-Higashi 2-chome, Fujisawa-
 shi, Kanagawa 251-0012, Japan
 ARIKAWA, Yasuyoshi, c/o Chordia Therapeutics Inc., 26-1, Muraoka- , Higashi 2-chome, Fujisawa-shi,
 Kanagawa 251-0012, Japan

(74) Fuldmægtig i Danmark: **AWA Denmark A/S, Strandgade 56, 1401 København K, Danmark**

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(56) Fremdragne publikationer:

EP-A2- 1 464 335

WO-A1-2016/193939

WO-A2-2016/142855

JP-A- 2016 533 379

ITO, M. ET AL.: "Discovery of 3-Benzyl-1-(trans-4- ((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-arylurea derivatives as novel and selective cyclin- dependent kinase 12 (CDK12) inhibitors", J. MED. CHEM., vol. 61, no. 17, 1 August 2018 (2018-08-01), pages 7710 - 7728, XP055618079, doi:10.1021/acs.jmedchem.8b00683
DATABASE REGISTRY 8 June 2008 (2008-06-08), retrieved from STN Database accession no. 1026426-87-8
DATABASE REGISTRY 4 December 2011 (2011-12-04), retrieved from STN Database accession no. 1348645-64-6

Description

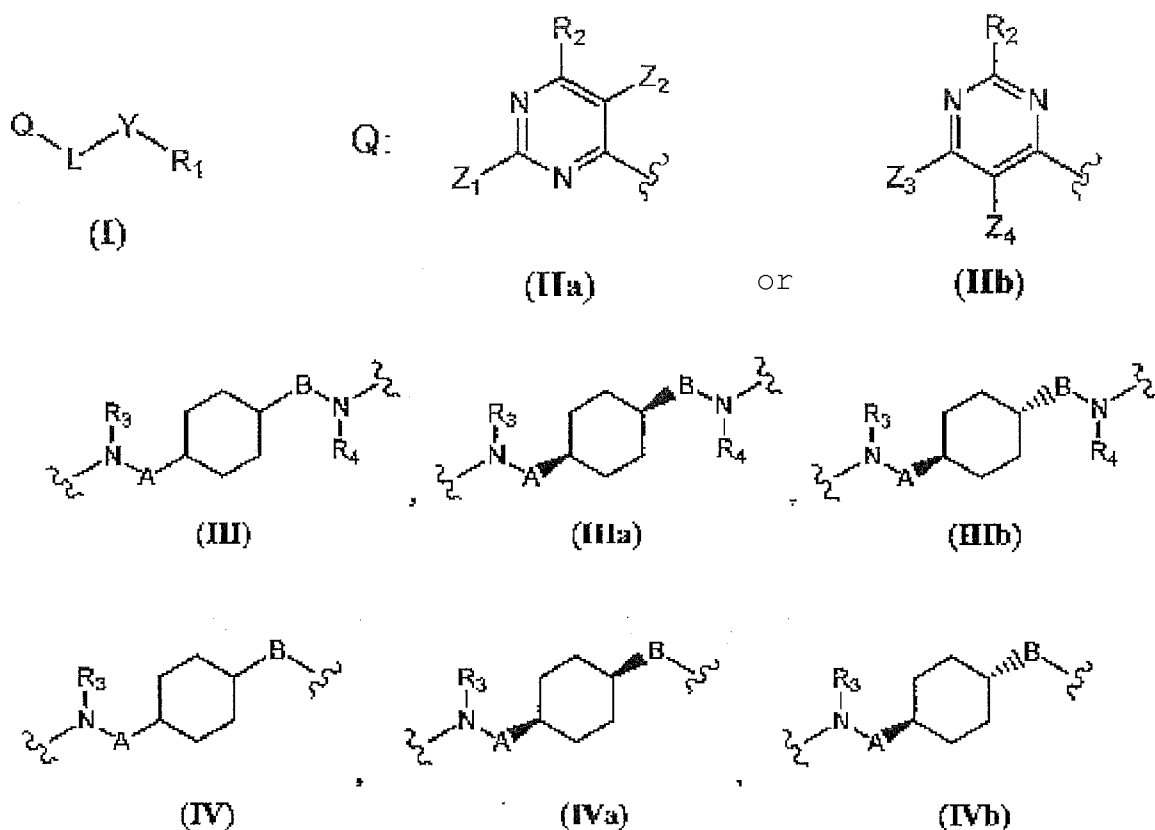
[Technical Field]

[0001] The present invention relates to a heterocyclic compound that may have a Cyclin-dependent kinase 12 (CDK12) inhibitory action, and is expected to be useful as a prophylactic or therapeutic drug for cancer and the like.

(Background of the Invention)

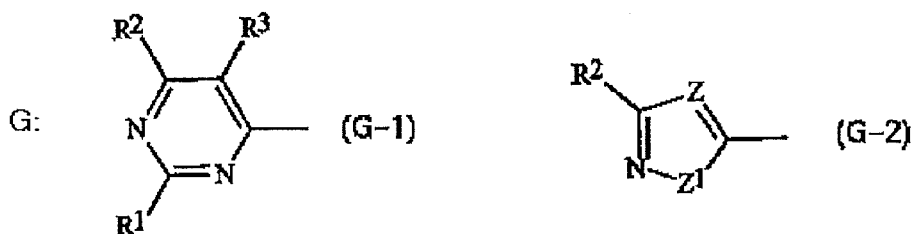
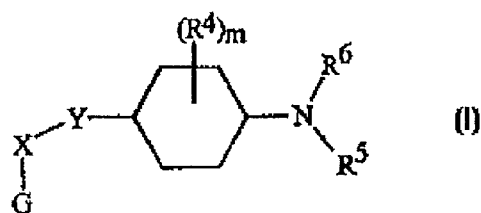
[0002] Cyclin-dependent kinase 12 (CDK12) is a serine/threonine kinase belonging to the CDK family. It becomes an active substance by binding to Cyclin K and transmits signals to the downstream. The process of copying the genetic information of DNA to messenger RNA (mRNA) is called "transcription". CDK12 is considered to be involved mainly in this transcription reaction and regulate the expression levels of various genes (non-patent document 1). CDK12 extends the transcription reaction of mRNA by phosphorylating the second serine (Ser2) at the C-terminal region of RNA polymerase II (non-patent document 2). In particular, CDK12 is considered to be involved in the transcription elongation reaction of genes with a long gene length, and affects the expression of BRCA1, ATM, FANCD2 genes and the like (non-patent document 3). All of these genes are a group of genes involved in DNA damage response (DDR), and are mainly involved in the maintenance of the stability of genomic DNA through the DNA repair mechanism. Inhibition of CDK12 decreases the expression of DDR-related genes, which in turn suppresses the DNA repair reaction. Therefrom it is considered that the damaged DNA of cancer cells cannot be repaired, and the growth and survival of the cancer cells can be suppressed. In particular, it has been shown that inhibition of both PARP involved in DNA repair and CDK12 completely suppresses the DNA repair reaction and induces cell death in cancer cells by a synthetic lethal action (non-patent document 4). From the foregoing, the action of inhibiting CDK12 is extremely useful for the prophylaxis and treatment of cancer.

[0003] Patent document 1 discloses the following compounds as compounds having an MCH receptor antagonistic action and useful for treating anxiety, depression, schizophrenia, obesity and the like.



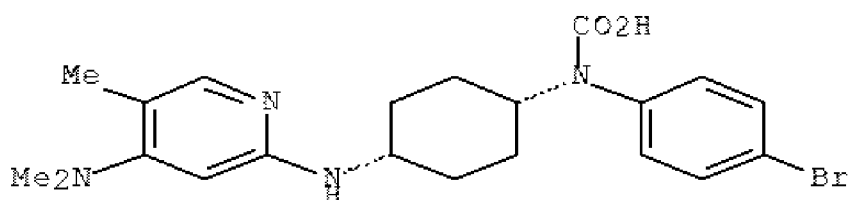
wherein each symbol is as defined in the document.

[0004] Patent document 2 discloses the following compounds as compounds useful as arthropodicide, fungicide and the like.

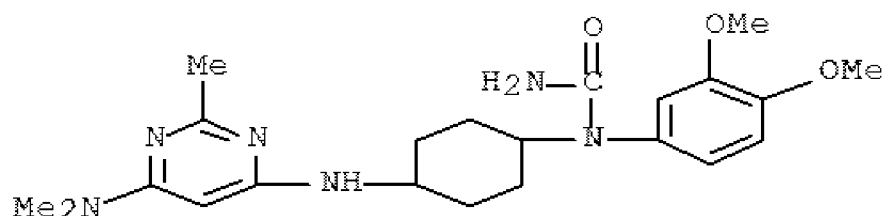


wherein each symbol is as defined in the document.

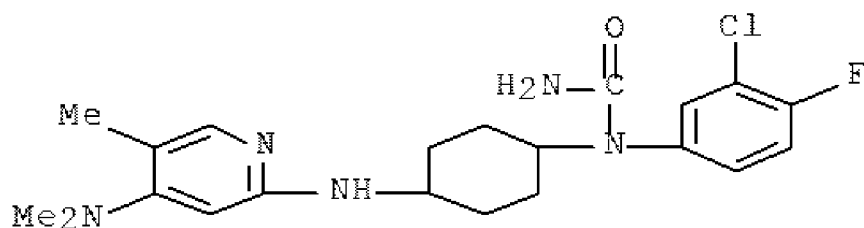
[0005] Non-patent document 5 discloses the following compound.



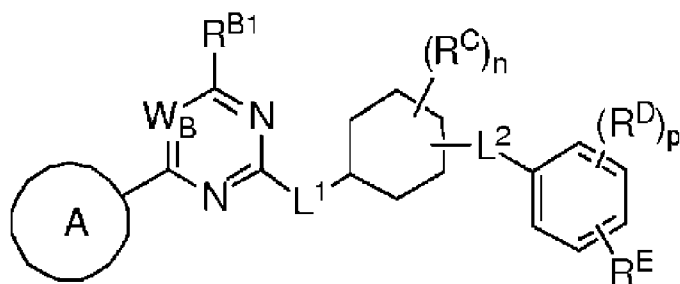
[0006] Non-patent document 6 discloses the following compound.



[0007] Non-patent document 7 discloses the following compound.



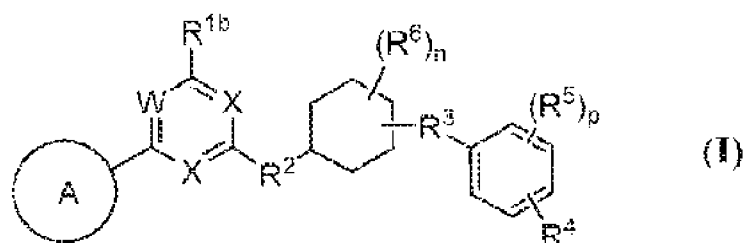
[0008] Patent document 3 discloses the following compound as a compound having a CDK7 inhibitory action (also capable of selectively inhibiting CDK7, CDK12 and/or CDK13) and useful for treating cancer, inflammatory diseases and the like.



(I)

wherein each symbol is as defined in the document.

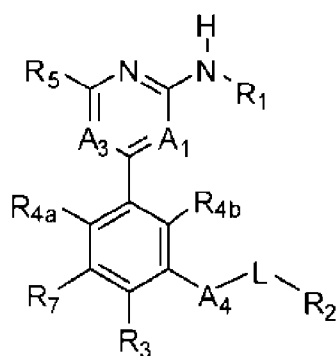
[0009] Patent document 4 discloses the following compound as a compound having a CDK7 inhibitory action (also capable of selectively inhibiting CDK7, CDK12 and/or CDK13) and useful for treating cancer, inflammatory diseases and the like.



(II)

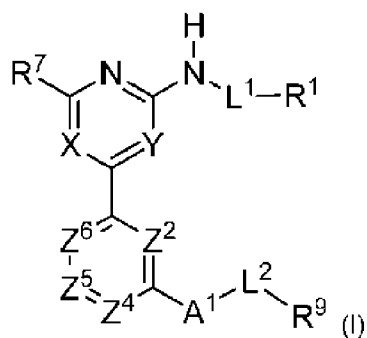
wherein each symbol is as defined in the document.

[0010] Patent document 5 discloses the following compound as a compound having a CDK9 (CDK1 - 9) inhibitory action and useful for treating cancer, inflammation, HIV and the like.



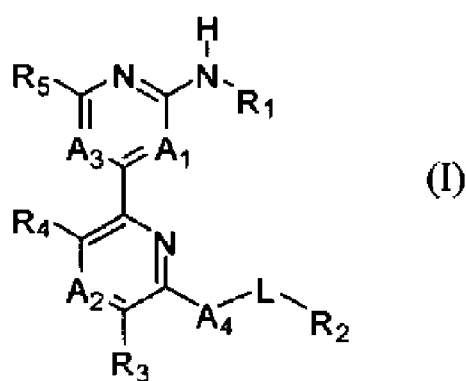
wherein each symbol is as defined in the document.

[0011] Patent document 6 discloses the following compound as a compound having a CDK9 (CDK1 - 9) inhibitory action and useful for treating cancer and the like.



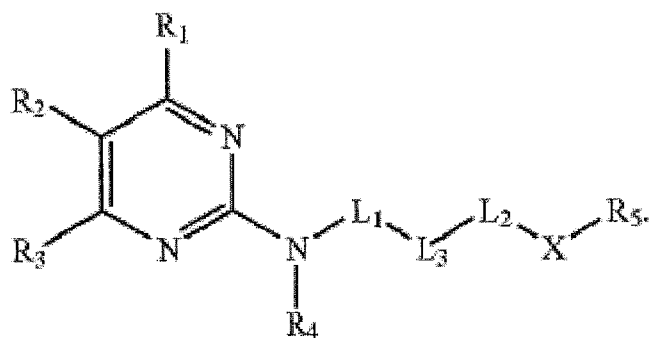
wherein each symbol is as defined in the document.

[0012] Patent document 7 discloses the following compound as a compound having a CDK9 (CDK1 - 9) inhibitory action and useful for treating cancer, inflammation, HIV and the like.



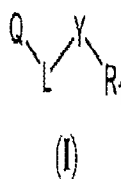
wherein each symbol is as defined in the document.

[0013] Patent document 8 discloses the following compound as a compound having a chemokine receptor CXCR3, CXCR4 inhibitory action and useful for treating cancer, inflammation and the like.

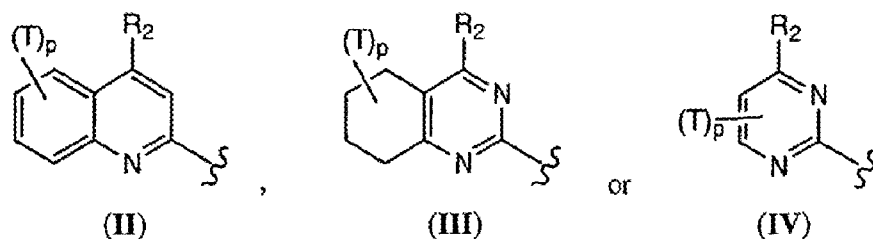


wherein each symbol is as defined in the document.

Patent document 9 discloses the following compounds

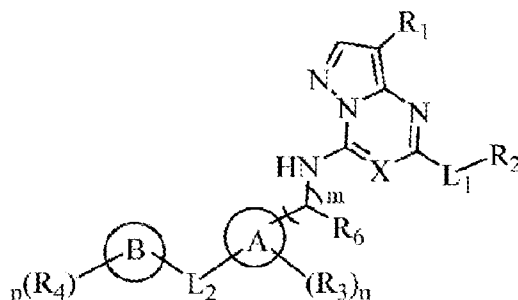


wherein Q is:

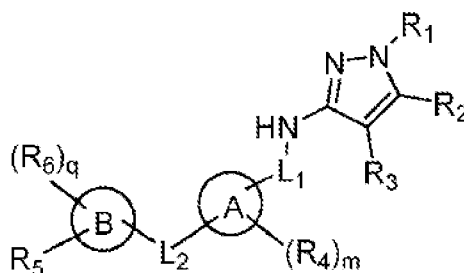


which act as MCH receptor antagonists. These compositions are useful in pharmaceutical compositions whose use includes prophylaxis or treatment of improving memory function, sleeping and arousal, anxiety, depression, mood disorders, seizure, obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, binge eating disorders including bulimia, anorexia, mental disorders including manic depression, schizophrenia, delirium, dementia, stress, cognitive disorders, attention deficit disorder, substance abuse disorders and dyskinesias including Parkinson's disease, epilepsy, and addiction.

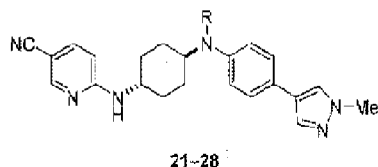
Patent document 10 discloses substituted pyrazolo[1,5-a][1,3,5]triazine and pyrazolo[1,5-a]pyrimidine derivatives of the following compound, which are therapeutically useful, particularly as selective transcriptional CDK inhibitors including CDK7, CDK9, CDK12, CDK13 and CDK18, more particularly transcriptional CDK7 inhibitors wherein X, ring A, ring B, L1, L2, R1, R2, R3, R4, R6, m, n and p have the meanings given in the specification and pharmaceutically acceptable salts thereof that are useful in the treatment and prevention of diseases or disorder associated with selective transcriptional CDKs in a mammal.



Patent document 11 discloses compounds which inhibit the activity of selective transcriptional cyclin dependent kinases (CDKs) including CDK7, CDK9, CDK12, CDK13 and CDK18, more particularly transcriptional cyclin dependent kinase-7 (CDK7).



[0014] Non-patent document 8 discloses the following compounds as selective cyclin dependency kinase 12 (CDK12) inhibitors.



21 (R = Ac)

23 (R = phenylpropionyl)

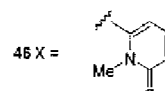
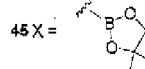
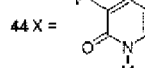
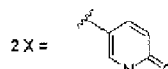
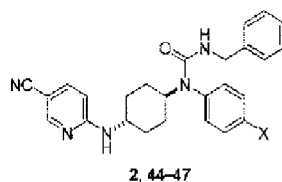
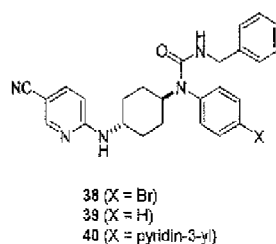
24 (R = methoxycarbonyl)

25 (R = benzylloxycarbonyl)

26 (R = ethylamino carbonyl)

27 (R = benzylamino carbonyl)

28 (R = cyclohexylamino carbonyl)



[Document List]

[Patent documents]

[0015]

patent document 1: JP2007091649A

patent document 2: WO 99/31072

patent document 3: WO 2015/058140A1

patent document 4: WO 2016/058544A1

patent document 5: WO 2012/066065A1

patent document 6: WO 2012/101065A2

patent document 7: WO 2011/012661A1

patent document 8: US2009/0143302A1

patent document 9: EP 1464335A1

patent document 10: WO 2016/142855A1

patent document 11: WO 2016/193939A1

[non-patent document]

[0016]

non-patent document 1: Bartkowiak B. et al., Genes Dev., 2010, 24, 2303-2316

non-patent document 2: Ekumi KM. et al., Nucleic Acids Res., 2015, 43, 2575-2589

non-patent document 3: Blazek D. et al., Genes Dev., 2011, 25, 2158-2172

non-patent document 4: Bajrami I. et al., Cancer Res., 2014, 74, 287-297

non-patent document 5: RN 1348645-64-6 REGISTRY

non-patent document 6: RN 1026673-82-4 REGISTRY

non-patent document 7: RN 1026426-87-8 REGISTRY

non-patent document 8: Ito M. et al., J. Med. Chem., 2018, 61, 7710-7728

[Summary of Invention]

[Technical Problem]

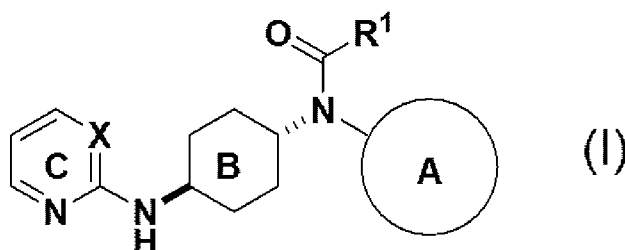
[0017] The present invention aims to provide a novel compound that may have a CDK12 inhibitory action, and is expected to be useful as a prophylactic or therapeutic drug for cancer and the like, and a medicament containing same.

[Solution to Problem]

[0018] The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound represented by the following formula (I) may have a CDK12 inhibitory action, which resulted in the completion of the present invention.

[0019] That is, the present invention is as described below.

[1] A compound represented by the formula (I):



wherein

X is CH or N;

R¹ is an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted heterocyclic group, or -NR²R³;

R² is a hydrogen atom or a substituent;

R³ is a substituent;

ring A is an optionally further substituted aromatic ring;

ring B is an optionally further substituted cyclohexane ring;

ring C is an optionally further substituted 6-membered nitrogen-containing aromatic heterocycle,

or a salt thereof (sometimes to be abbreviated as "compound (I)" in the present specification).

[2] The compound of [1], wherein the ring C is an optionally further substituted pyridine ring (that is, X is CH).

[3] The compound of [1], wherein the ring C is an optionally further substituted pyrimidine ring (that is, X is N).

[4] The compound of [3], wherein the ring A is an optionally further substituted C₆₋₁₄ aromatic hydrocarbon ring.

[5] The compound of [3], wherein the ring A is an optionally further substituted 5- to 14-membered aromatic heterocycle.

[6] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group, an optionally substituted C₆₋₁₄ aryloxy group and an optionally substituted 5- to 14-membered aromatic heterocyclic group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group and an optionally substituted 5- to 14-membered aromatic heterocyclic group, (3) an optionally substituted C₆₋₁₄ aryl group, (4) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group, R³ is (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted 3- to 14-membered non-aromatic heterocyclic group and an optionally substituted 5- to 14-membered aromatic heterocyclic group or (ii) an optionally substituted C₆₋₁₄ aryl group;

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from (1) a halogen atom, (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group, (5) an optionally substituted C₂₋₆ alkenyl group, (6) an optionally substituted C₆₋₁₄ aryl group, (7) an optionally substituted C₁₋₆ alkoxy group, (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure) and (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group;

ring B is a cyclohexane ring not substituted further; and

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N) each of which is optionally further substituted by 1 to 3 substituents selected from (1) a halogen atom, (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group, (4) an optionally substituted C₆₋₁₄ aryl group, (5) an optionally substituted C₁₋₆ alkoxy group, (6) an optionally substituted C₆₋₁₄ aryloxy group, (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group, (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group.

[7] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group optionally substituted by 1 to 3 halogen atoms, a C₆₋₁₄ aryloxy group and a 5- to 14-membered aromatic heterocyclic group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group and a 5- to 14-membered aromatic heterocyclic group, (3) a C₆₋₁₄ aryl group, (4) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₆₋₁₄ aryl groups, or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by 1 to 3 C₆₋₁₄ aryl groups, R³ is (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a C₃₋₁₀ cycloalkyl group, (b) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C₁₋₆ alkoxy group, a C₁₋₆ alkylsulfonyl group and a C₁₋₆ alkylsulfonylamino group, (c) a 3- to 14-membered non-aromatic heterocyclic group, and (d) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group and a C₁₋₆ alkoxy group, or (ii) a C₆₋₁₄ aryl group];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from (1) a halogen atom, (2) a cyano group, (3) a hydroxy group, (4) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a C₁₋₆ alkoxy group and (c) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, (5) a C₂₋₆ alkenyl group, (6) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a cyano group, (c) a C₁₋₆ alkoxy group and (d) a carbamoyl group, (7) a C₁₋₆ alkoxy group, (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 C₁₋₆ alkoxy groups, (b) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from a cyano group and a C₁₋₆ alkoxy group, and (c) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, (9) a carboxy group, (10) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group, (11) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a cyano group, (c) a C₁₋₆ alkyl group, (d) a C₁₋₆ alkoxy group, (e) a C₁₋₆ alkyl-carbonyl group, (f) a carbamoyl group, (g) a mono- or di-C₁₋₆ alkylamino group and (h) a C₁₋₆ alkylsulfonyl group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure) and (12) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a hydroxy group, a C₁₋₆ alkoxy group, a carbamoyl group, a 3- to 14-membered non-aromatic heterocyclic group and a 5- to 14-membered aromatic heterocyclic group, (c) a C₁₋₆ alkoxy group, (d) an amino group, (e) a carboxy group, (f) a C₁₋₆ alkoxy-carbonyl group, (g) a carbamoyl group and (h) a 3- to 14-membered non-aromatic heterocyclic group;

ring B is a cyclohexane ring not substituted further;

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N) each of which is optionally further substituted by 1 to 3 substituents selected from (1) a halogen atom, (2) a cyano group, (3) C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (4) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a cyano group, (c) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (d) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (e) a mono- or di-C₁₋₆ alkylamino group, (f) a C₁₋₆ alkyl-carbonylamino group, (g) a C₁₋₆ alkyl-carbonyl group, (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group, (5) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom and (b) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, (6) a C₆₋₁₄ aryloxy group optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups, (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group, (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (i) a halogen atom, (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (vii) a mono- or di-C₁₋₆ alkylamino group, (viii) a

C₁₋₆ alkyl-carbonylamino group, (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group, (xi) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group and (xii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₃₋₁₀ cycloalkyl group and a (C₁₋₆ alkyl) (C₁₋₆ alkyl-sulfonyl) amino group, (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups and a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure), (c) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups, (d) a C₃₋₁₀ cycloalkyl-carbonyl group, (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and a C₁₋₆ alkyl group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (f) a 5- to 14-membered aromatic heterocyclic group, (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom, (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group and a C₁₋₆ alkoxy group, (f) a C₃₋₁₀ cycloalkyl group, (g) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (h) a C₁₋₆ alkyl-carbonyl group, (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group, (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group, (l) a dimethyl(oxide)-λ⁶-sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (11) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom, (e) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₁₋₆ alkoxy-carbonyl group and a carbamoyl group, (f) a C₁₋₆ alkoxy group, (g) a C₁₋₆ alkoxy-carbonyl group, (h) a C₁₋₆ alkylsulfonyl group and (i) a 3- to 14-membered non-aromatic heterocyclic group.

[8] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group, a C₆₋₁₄ aryloxy group and a 5- to 14-membered aromatic heterocyclic group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group and a 5- to 14-membered aromatic heterocyclic group, or (3) -NR²R³ [R² is a hydrogen atom, and R³ is a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 halogen atoms and (b) a 5- to 14-membered aromatic heterocyclic group];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group and (c) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkoxy group;

ring B is a cyclohexane ring not substituted further; and

ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 to 3 substituents selected from (1) a cyano group, (2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (3) a 3- to 14-membered non-aromatic heterocyclic-oxy group, (4) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group and (c) a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (6) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen atom, (c) a C₁₋₆ alkyl group and (d) a C₁₋₆ alkylsulfonyl group.

[9] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₄ aryl group and an optionally substituted C₆₋₁₄ aryloxy group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, an optionally substituted C₃₋₁₀ cycloalkyl

group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted amino group, an optionally substituted 3- to 14-membered non-aromatic heterocyclic group and an optionally substituted 5- to 14-membered aromatic heterocyclic group, (3) an optionally substituted C₆₋₁₄ aryl group, (4) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group and an optionally substituted C₆₋₁₄ aryl group or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group, and R³ is (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted amino group, an optionally substituted 3- to 14-membered non-aromatic heterocyclic group and an optionally substituted 5- to 14-membered aromatic heterocyclic group, (ii) an optionally substituted C₃₋₁₀ cycloalkyl group or (iii) an optionally substituted C₆₋₁₄ aryl group];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from (1) a halogen atom, (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group, (5) an optionally substituted C₂₋₆ alkenyl group, (6) an optionally substituted C₆₋₁₄ aryl group, (7) an optionally substituted C₁₋₆ alkoxy group, (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure) and (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group;

ring B is a cyclohexane ring not substituted further; and

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N) each of which is optionally further substituted by 1 to 3 substituents selected from (1) a halogen atom, (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group, (4) an optionally substituted C₆₋₁₄ aryl group, (5) an optionally substituted C₁₋₆ alkoxy group, (6) an optionally substituted C₆₋₁₄ aryloxy group, (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group, (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group.

[10] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a C₃₋₁₀ cycloalkyl group, a C₁₋₆ alkoxy group, and a C₆₋₁₄ aryloxy group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and an amino group, (d) a C₆₋₁₄ aryl group, (e) a C₁₋₆ alkoxy group, (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group, (g) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 halogen atoms and (h) a 5- to 14-membered aromatic heterocyclic group, (3) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a C₆₋₁₄ aryl group or (4) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group, and R³ is (i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and an amino group, (d) a C₁₋₆ alkoxy group, (e) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 halogen atoms, (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group, (g) a 3- to 14-membered non-aromatic heterocyclic group and (h) a 5- to 14-membered aromatic heterocyclic group, or (ii) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 halogen atoms];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from (1) a halogen atom, (2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom and (b) a C₃₋₁₀ cycloalkyl group, (3) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a C₁₋₆ alkoxy group and (c) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group, (4) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group optionally substituted by a C₁₋₆ alkoxy group, (5) a 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure) and (6) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a C₃₋₁₀ cycloalkyl group and a 3- to 14-membered

non-aromatic heterocyclic group, (c) a C₃₋₁₀ cycloalkyl group, (d) a C₁₋₆ alkoxy group, (e) an amino group, (f) a carboxy group, (g) a C₁₋₆ alkoxy-carbonyl group and (h) a 3- to 14-membered non-aromatic heterocyclic group; ring B is a cyclohexane ring not substituted further;

ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 to 3 substituents selected from (1) a halogen atom, (2) a cyano group, (3) C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (4) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a cyano group, (c) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (d) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (e) a mono- or di-C₁₋₆ alkylamino group, (f) a C₁₋₆ alkyl-carbonylamino group, (g) a C₁₋₆ alkyl-carbonyl group, (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group, (5) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a 3- to 14-membered non-aromatic heterocyclic group and (c) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, (6) a C₆₋₁₄ aryloxy group optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups, (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (i) a halogen atom, (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (vii) a mono- or di-C₁₋₆ alkylamino group, (viii) a C₁₋₆ alkyl-carbonylamino group, (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group, (xi) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group and (xii) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₃₋₁₀ cycloalkyl group and a (C₁₋₆ alkyl) (C₁₋₆ alkyl-sulfonyl) amino group, (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group, a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups and a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure), (c) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups, (d) a C₃₋₁₀ cycloalkyl-carbonyl group, (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and a C₁₋₆ alkyl group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (f) a 5- to 14-membered aromatic heterocyclic group, (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom, (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group and a C₁₋₆ alkoxy group, (f) a C₃₋₁₀ cycloalkyl group, (g) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, (h) a C₁₋₆ alkyl-carbonyl group, (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group, (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group, (l) a dimethyl (oxide)-λ⁶-sulfanylidene-amino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (11) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom, (e) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₁₋₆ alkoxy-carbonyl group and a carbamoyl group, (f) a C₃₋₁₀ cycloalkyl group, (g) a C₁₋₆ alkoxy group, (h) a C₁₋₆ alkoxy-carbonyl group, (i) a C₁₋₆ alkylsulfonyl group and (j) a 3- to 14-membered non-aromatic heterocyclic group.

[11] The compound of [1], wherein

R¹ is (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a C₁₋₆ alkoxy group and a C₆₋₁₄ aryloxy group, (2) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group, (c) a C₆₋₁₄ aryl group, (d) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group and (e) a 5- to 14-membered aromatic heterocyclic group or (3) -NR²R³ [R² is a hydrogen atom, and R³ is a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 halogen atoms, (d) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 halogen atoms and (e) a 5- to 14-membered aromatic heterocyclic group];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring or a 5- to 14-membered aromatic heterocycle each of which is optionally further substituted by 1 - 5 substituents selected from a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group and

(c) a C₁₋₆ alkoxy group;
 ring B is a cyclohexane ring not substituted further; and
 ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 to 3 substituents selected from (1)
 a cyano group, (2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, (3) a 3- to 14-membered
 non-aromatic heterocyclic-oxy group, (4) an amino group optionally mono- or di-substituted by substituent(s)
 selected from (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered
 non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (the 3- to 14-membered non-
 aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro
 ring structure), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 sub-
 stituents selected from (a) a halogen atom, (b) a hydroxy group and (c) a C₁₋₆ alkyl group optionally substituted
 by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a
 bicyclo ring structure, a bridged ring structure, or a spiro ring structure) and (6) a 5- to 14-membered aromatic
 heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen
 atom, (c) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms and (d) a C₁₋₆ alkylsulfonyl group.

[12] A medicament comprising the compound of [1] or a salt thereof.

[13] The medicament of [12], for use as a CDK12 inhibitor.

[14] The medicament of [12], for use as a prophylactic or therapeutic drug for cancer.

[Advantageous Effects of Invention]

[0020] The compound of the present invention may have a CDK12 inhibitory action, and may be useful as a medicament such as a prophylactic or therapeutic drug for cancer and the like.

[Brief Description of Drawings]

[0021] Fig. 1 shows the binding of BODIPY-FL-labeled AT-7519 to CDK12/CycK protein by TR-FRET. Black and white circles show TR-FRET signals in the absence and presence of 2 μ M AT-7519, respectively.

(Detailed Description of the Invention)

[0022] The definition of each substituent used in the present specification is described in detail in the following. Unless otherwise specified, each substituent has the following definition.

[0023] In the present specification, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

[0024] In the present specification, examples of the "C₁₋₆ alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

[0025] In the present specification, examples of the "C₁₋₁₂ alkyl group" include heptyl, octyl, nonyl, decyl, undecyl, and dodecyl in addition to the above-mentioned "C₁₋₆ alkyl group".

[0026] In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl group" include a C₁₋₆ alkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, propyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

[0027] In the present specification, examples of the "C₂₋₆ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

[0028] In the present specification, examples of the "C₂₋₆ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and 4-methyl-2-pentylnyl.

[0029] In the present specification, examples of the "C₃₋₁₀ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

[0030] In the present specification, examples of the "optionally halogenated C₃₋₁₀ cycloalkyl group" include a C₃₋₁₀ cycloalkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include cyclopropyl, 2,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0031] In the present specification, examples of the "C₃₋₁₀ cycloalkenyl group" include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

[0032] In the present specification, examples of the "C₆₋₁₄ aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

[0033] In the present specification, examples of the "C₇₋₁₆ aralkyl group" include benzyl, phenethyl, naphthylmethyl and phenylpropyl.

[0034] In the present specification, examples of the "C₁₋₆ alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

[0035] In the present specification, examples of the "optionally halogenated C₁₋₆ alkoxy group" include a C₁₋₆ alkoxy group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy and hexyloxy.

[0036] In the present specification, examples of the "C₃₋₁₀ cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

[0037] In the present specification, examples of the "C₁₋₆ alkylthio group" include methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio.

[0038] In the present specification, examples of the "optionally halogenated C₁₋₆ alkylthio group" include a C₁₋₆ alkylthio group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

[0039] In the present specification, examples of the "C₁₋₆ alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

[0040] In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl-carbonyl group" include a C₁₋₆ alkyl-carbonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include acetyl, chloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

[0041] In the present specification, examples of the "C₁₋₆ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

[0042] In the present specification, examples of the "C₆₋₁₄ aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

[0043] In the present specification, examples of the "C₇₋₁₆ aralkyl-carbonyl group" include phenylacetyl and phenylpropionyl.

[0044] In the present specification, examples of the "5- to 14-membered aromatic heterocyclylcarbonyl group" include nicotinoyl, isonicotinoyl, thenoyl and furoyl.

[0045] In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclylcarbonyl group" include morpholinylcarbonyl, piperidinylcarbonyl and pyrrolidinylcarbonyl.

[0046] In the present specification, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-ethyl-N-methylcarbamoyl.

[0047] In the present specification, examples of the "mono- or di-C₇₋₁₆ aralkyl-carbamoyl group" include benzylcarbamoyl and phenethylcarbamoyl.

[0048] In the present specification, examples of the "C₁₋₆ alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl and tert-butylsulfonyl.

[0049] In the present specification, examples of the "optionally halogenated C₁₋₆ alkylsulfonyl group" include a C₁₋₆ alkylsulfonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl and hexylsulfonyl.

[0050] In the present specification, examples of the "C₆₋₁₄ arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl and 2-naphthylsulfonyl.

[0051] In the present specification, examples of the "substituent" include a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an acyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl group, an optionally substituted hydroxy group, an optionally substituted sulfanyl (SH) group and an optionally substituted silyl group.

[0052] In the present specification, examples of the "hydrocarbon group" (including "hydrocarbon group" of "optionally substituted hydrocarbon group") include a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group.

[0053] In the present specification, examples of the "optionally substituted hydrocarbon group" include a hydrocarbon group optionally having substituent(s) selected from the following substituent group A.

[substituent group A]

[0054]

- 5 (1) a halogen atom,
- (2) a nitro group,
- (3) a cyano group,
- (4) an oxo group,
- (5) a hydroxy group,
- 10 (6) an optionally halogenated C₁₋₆ alkoxy group,
- (7) a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthoxy),
- (8) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy),
- (9) a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy),
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group (e.g., morpholinyl, piperidinyl),
- 15 (11) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- (12) a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),
- (13) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),
- 20 (15) a C₆₋₁₄ aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy),
- (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy),
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., morpholinylcarbonyloxy, piperidinylcarbonyloxy),
- 25 (18) an optionally halogenated C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, trifluoromethylsulfonyloxy),
- (19) a C₆₋₁₄ arylsulfonyloxy group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonyloxy, toluenesulfonyloxy),
- (20) an optionally halogenated C₁₋₆ alkylthio group,
- (21) a 5- to 14-membered aromatic heterocyclic group,
- 30 (22) a 3- to 14-membered non-aromatic heterocyclic group,
- (23) a formyl group,
- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- (26) a C₆₋₁₄ aryl-carbonyl group,
- 35 (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
- (28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- (30) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl),
- (31) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),
- 40 (32) a carbamoyl group,
- (33) a thiocarbamoyl group,
- (34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
- (35) a C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl),
- (36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl, thienylcarbamoyl),
- 45 (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group (e.g., morpholinylcarbamoyl, piperidinylcarbamoyl),
- (38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- (39) a C₆₋₁₄ arylsulfonyl group,
- (40) a 5- to 14-membered aromatic heterocyclylsulfonyl group (e.g., pyridylsulfonyl, thienylsulfonyl),
- 50 (41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
- (42) a C₆₋₁₄ arylsulfinyl group (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl),
- (43) a 5- to 14-membered aromatic heterocyclylsulfinyl group (e.g., pyridylsulfinyl, thienylsulfinyl),
- (44) an amino group,
- (45) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
- 55 (46) a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino),
- (47) a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino),
- (48) a C₇₋₁₆ aralkylamino group (e.g., benzylamino),

- (49) a formylamino group,
 (50) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino, propanoylamino, butanoylamino),
 (51) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino),
 (52) a C₆₋₁₄ aryl-carbonylamino group (e.g., phenylcarbonylamino, naphthylcarbonylamino),
 (53) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),
 (54) a C₇₋₁₆ aralkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino),
 (55) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
 (56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonylamino, toluenesulfonylamino),
 (57) an optionally halogenated C₁₋₆ alkyl group,
 (58) a C₂₋₆ alkenyl group,
 (59) a C₂₋₆ alkynyl group,
 (60) a C₃₋₁₀ cycloalkyl group,
 (61) a C₃₋₁₀ cycloalkenyl group and
 (62) a C₆₋₁₄ aryl group.

[0055] The number of the above-mentioned substituents in the "optionally substituted hydrocarbon group" is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0056] In the present specification, examples of the "heterocyclic group" (including "heterocyclic group" of "optionally substituted heterocyclic group") include (i) an aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0057] In the present specification, examples of the "aromatic heterocyclic group" (including "5- to 14-membered aromatic heterocyclic group") include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0058] Preferable examples of the "aromatic heterocyclic group" include 5- or 6-membered monocyclic aromatic heterocyclic groups such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, triazinyl and the like; and

8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocyclic groups such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, imidazopyridinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyrazinyl, imidazopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrazolotriazinyl, naphtho[2,3-b]thienyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

[0059] In the present specification, examples of the "non-aromatic heterocyclic group" (including "3- to 14-membered non-aromatic heterocyclic group") include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0060] Preferable examples of the "non-aromatic heterocyclic group" include 3- to 8-membered monocyclic non-aromatic heterocyclic groups such as aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranly, pyrrolinyl, pyrrolidinyl, imidazoliny, imidazolidinyl, oxazoliny, oxazolidinyl, pyrazoliny, pyrazolidinyl, thiazoliny, thiazolidinyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisooxazolyl, piperidinyl, piperazinyl, tetrahydropyridinyl, dihydropyridinyl, dihydrothiopyranyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, azepinyl, oxepanyl, azocanyl, diazocanyl and the like; and

9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocyclic groups such as dihydrobenzofuranly, dihydrobenzimidazolyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, dihydrobenzisothiazolyl, dihydronaphtho[2,3-b]thienyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 4H-quinoliziny, indoliny, isoindoliny, tetrahydrothieno[2,3-c]pyridinyl, tetrahydrobenzazepinyl, tetrahydroquinoxalinyl, tetrahydrophenanthridinyl, hexahydrophenothiazinyl, hexahydrophenoxazinyl, tetrahydrophthalazinyl, tetrahydronaphthyridinyl, tetrahydroquinazolinyl, tetrahydrocinnolinyl, tetrahydrocarbazolyl, tetrahydro- β -carbolinyl, tetrahydroacridinyl, tetrahydrophenazinyl, tetrahydrothioxanthinyl, octahydroisoquinolyl and the like.

[0061] In the present specification, preferable examples of the "7- to 10-membered bridged heterocyclic group" include

quinuclidinyl and 7-azabicyclo[2.2.1]heptanyl.

[0062] In the present specification, examples of the "nitrogen-containing heterocyclic group" include a "heterocyclic group" containing at least one nitrogen atom as a ring-constituting atom.

[0063] In the present specification, examples of the "optionally substituted heterocyclic group" include a heterocyclic group optionally having substituent(s) selected from the aforementioned substituent group A.

[0064] The number of the substituents in the "optionally substituted heterocyclic group" is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0065] In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfinio group, a sulfo group, a sulfamoyl group and a phosphono group, each optionally having "1 or 2 substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a 5- to 14-membered aromatic heterocyclic group and a 3- to 14-membered non-aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom, an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group and a carbamoyl group".

[0066] Examples of the "acyl group" also include a hydrocarbon-sulfonyl group, a heterocyclylsulfonyl group, a hydrocarbon-sulfinyl group and a heterocyclylsulfinyl group.

[0067] Here, the hydrocarbon-sulfonyl group means a hydrocarbon group-bonded sulfonyl group, the heterocyclylsulfonyl group means a heterocyclic group-bonded sulfonyl group, the hydrocarbon-sulfinyl group means a hydrocarbon group-bonded sulfinyl group and the heterocyclylsulfinyl group means a heterocyclic group-bonded sulfinyl group.

[0068] Preferable examples of the "acyl group" include a formyl group, a carboxy group, a C₁₋₆ alkyl-carbonyl group, a C₂₋₆ alkenyl-carbonyl group (e.g., crotonoyl), a C₃₋₁₀ cycloalkyl-carbonyl group (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a C₃₋₁₀ cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5-to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl), a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl), a sulfinio group, a C₁₋₆ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl), a sulfo group, a C₁₋₆ alkylsulfonyl group, a C₆₋₁₄ arylsulfonyl group, a phosphono group and a mono- or di-C₁₋₆ alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono).

[0069] In the present specification, examples of the "optionally substituted amino group" include an amino group optionally having "1 or 2 substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

[0070] Preferable examples of the optionally substituted amino group include an amino group, a mono- or di-(optionally halogenated C₁₋₆ alkyl)amino group (e.g., methylamino, trifluoromethylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), a mono- or di-C₂₋₆ alkenylamino group (e.g., diallylamino), a mono- or di-C₃₋₁₀ cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino), a mono- or di-C₇₋₁₆ aralkylamino group (e.g., benzylamino, dibenzylamino), a mono- or di-(optionally halogenated C₁₋₆ alkyl)-carbonylamino group (e.g., acetylamino, propionylamino), a mono- or di-C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), a mono- or di-C₇₋₁₆ aralkyl-carbonylamino group (e.g., benzylcarbonylamino), a mono- or di-5- to 14-membered aromatic heterocyclylcarbonylamino group (e.g., nicotinoylamino, isonicotinoylamino), a mono- or di-3- to 14-membered non-aromatic heterocyclylcarbonylamino group (e.g., piperidinylcarbonylamino), a mono- or di-C₁₋₆ alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino), a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino), a carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl)amino group (e.g., methylcarbamoylamino), a (mono- or di-C₇₋₁₆ aralkyl-carbamoyl) amino group (e.g., benzylcarbamoylamino), a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino), a C₆₋₁₄ arylsulfonylamino group (e.g., phenylsulfonylamino), a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl)amino group (e.g., N-acetyl-N-methylamino) and a (C₁₋₆ alkyl) (C₆₋₁₄ aryl-carbonyl) amino group (e.g., N-

benzoyl-N-methylamino).

[0071] In the present specification, examples of the "optionally substituted carbamoyl group" include a carbamoyl group optionally having "1 or 2 substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 selected from substituent group A".

[0072] Preferable examples of the optionally substituted carbamoyl group include a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl, cyclohexylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (e.g., acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-carbamoyl group (e.g., benzoylcarbamoyl) and a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl).

[0073] In the present specification, examples of the "optionally substituted thiocarbamoyl group" include a thiocarbamoyl group optionally having "1 or 2 substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

[0074] Preferable examples of the optionally substituted thiocarbamoyl group include a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, ethylthiocarbamoyl, dimethylthiocarbamoyl, diethylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-thiocarbamoyl group (e.g., acetylthiocarbamoyl, propionylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-thiocarbamoyl group (e.g., benzoylthiocarbamoyl) and a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl).

[0075] In the present specification, examples of the "optionally substituted sulfamoyl group" include a sulfamoyl group optionally having "1 or 2 substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

[0076] Preferable examples of the optionally substituted sulfamoyl group include a sulfamoyl group, a mono- or di-C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (e.g., phenylsulfamoyl), a mono- or di-C₇₋₁₆ aralkyl-sulfamoyl group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl) and a 5- to 14-membered aromatic heterocyclylsulfamoyl group (e.g., pyridylsulfamoyl).

[0077] In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxyl group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonoyl group and a C₆₋₁₄ arylsulfonoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

[0078] Preferable examples of the optionally substituted hydroxy group include a hydroxy group, a C₁₋₆ alkoxy group, a C₂₋₆ alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenylloxy, 3-hexenyloxy), a C₃₋₁₀ cycloalkyloxy group (e.g., cyclohexyloxy), a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthyloxy), a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy, phenethylloxy), a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy), a C₇₋₁₆ aralkyl-carbonyloxy group (e.g., benzylcarbonyloxy), a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy), a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., piperidinylcarbonyloxy), a C₁₋₆ alkoxy-carbonyloxy group (e.g., tert-butoxycarbonyloxy), a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy), a carbamoyloxy group, a C₁₋₆ alkyl-carbamoyloxy group (e.g., meth-

ylcarbamoyloxy), a C₇₋₁₆ aralkyl-carbamoyloxy group (e.g., benzylcarbamoyloxy), a C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy) and a C₆₋₁₄ arylsulfonyloxy group (e.g., phenylsulfonyloxy).

[0079] In the present specification, examples of the "optionally substituted sulfanyl group" include a sulfanyl group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group and a 5- to 14-membered aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from substituent group A" and a halogenated sulfanyl group.

[0080] Preferable examples of the optionally substituted sulfanyl group include a sulfanyl (-SH) group, a C₁₋₆ alkylthio group, a C₂₋₆ alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C₃₋₁₀ cycloalkylthio group (e.g., cyclohexylthio), a C₆₋₁₄ arylthio group (e.g., phenylthio, naphthylthio), a C₇₋₁₆ aralkylthio group (e.g., benzylthio, phenethylthio), a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C₆₋₁₄ aryl-carbonylthio group (e.g., benzoylthio), a 5- to 14-membered aromatic heterocyclylthio group (e.g., pyridylthio) and a halogenated thio group (e.g., pentafluorothio).

[0081] In the present specification, examples of the "optionally substituted silyl group" include a silyl group optionally having "1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

[0082] Preferable examples of the optionally substituted silyl group include a tri-C₁₋₆ alkylsilyl group (e.g., trimethylsilyl, tert-butyl(dimethyl)silyl).

[0083] In the present specification, examples of the "hydrocarbon ring" include a C₆₋₁₄ aromatic hydrocarbon ring, C₃₋₁₀ cycloalkane and C₃₋₁₀ cycloalkene.

[0084] In the present specification, examples of the "C₆₋₁₄ aromatic hydrocarbon ring" include benzene and naphthalene.

[0085] In the present specification, examples of the "C₃₋₁₀ cycloalkane" include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane.

[0086] In the present specification, examples of the "C₃₋₁₀ cycloalkene" include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

[0087] In the present specification, examples of the "heterocycle" include an aromatic heterocycle and a non-aromatic heterocycle, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0088] In the present specification, examples of the "aromatic heterocycle" include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "aromatic heterocycle" include 5- or 6-membered monocyclic aromatic heterocycles such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, triazole, tetrazole, triazine and the like; and 8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocycles such as benzothiophene, benzofuran, benzimidazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzotriazole, imidazopyridine, thienopyridine, furopyridine, pyrrolopyridine, pyrazolopyridine, oxazolopyridine, thiazolopyridine, imidazopyrazine, imidazopyrimidine, thienopyrimidine, furopyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, oxazolopyrimidine, thiazolopyrimidine, pyrazolopyrimidine, pyrazolo-triazine, naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine, acridine, phenazine, phenothiazine, phenoxathiine and the like.

[0089] In the present specification, examples of the "non-aromatic heterocycle" include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "non-aromatic heterocycle" include 3- to 8-membered monocyclic non-aromatic heterocycles such as aziridine, oxirane, thiirane, azetidene, oxetane, thietane, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline, pyrazolidine, thiazoline, thiazolidine, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, piperazine, tetrahydropyridine, dihydropyridine, dihydrothiopyran, tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, azepane, diazepane, azepine, azocane, diazocane, oxepane and the like; and

9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocycles such as dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, 4H-quinolizine, indoline, isoindoline, tetrahydrothieno[2,3-c]pyridine, tetrahydrobenzazepine, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiazine, hexahydrophenoxazine, tetrahydrophthalazine, tetrahydronaphthyridine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro- β -carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxanthene, octahydroisoquinoline and the like.

[0090] In the present specification, examples of the "nitrogen-containing heterocycle" include a "heterocycle" containing at least one nitrogen atom as a ring-constituting atom.

[0091] In the present specification, examples of the "aromatic ring" of the "optionally further substituted aromatic ring" include the above-mentioned "C₆₋₁₄ aromatic hydrocarbon ring" and "aromatic heterocycle". As the substituent thereof, the above-mentioned "substituent" can be mentioned.

[0092] In the present specification, examples of the "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" include the above-mentioned "aromatic heterocycle" that is 6-membered and contains at least one nitrogen atom as the constituting atom. As the substituent thereof, the above-mentioned "substituent" can be mentioned.

[0093] The definition of each symbol in the formula (I) is explained below.

[0094] R¹ is an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted heterocyclic group, or -NR²R³; R² is a hydrogen atom or a substituent; and R³ is a substituent.

[0095] Examples of the "substituent" of the "optionally substituted C₁₋₆ alkyl group" for R¹ include an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl).

[0096] Examples of the "substituent" of the "optionally substituted C₁₋₆ alkoxy group" for R¹ include an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl).

[0097] Examples of the "heterocyclic group" of the "optionally substituted heterocyclic group" for R¹ include a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, tetrahydropyranyl). As the "substituent" thereof, an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) can be mentioned.

[0098] Examples of the "substituent" for R² include an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl).

[0099] Examples of the "substituent" for R³ include an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, neopentyl), and an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl).

[0100] R¹ is preferably

(1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (4) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), R³ is (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, neopentyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) or (ii) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl).

[0101] R¹ is more preferably,

(1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., chlorine atom), a C₆₋₁₄ aryloxy group (e.g., phenoxy) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) a C₆₋₁₄ aryl group (e.g., phenyl), (4) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, tetrahydropyranyl) optionally substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl) or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl), R³ is (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, neopentyl) optionally substituted by 1 to 3 substituents selected from (a) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), (b) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a cyano group, a C₁₋₆ alkoxy group (e.g., methoxy), a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino), (c) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl) and (d) a 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl) and a C₁₋₆ alkoxy group (e.g., methoxy) or (ii) a C₆₋₁₄ aryl group (e.g., phenyl)].

[0102] R¹ is further preferably,

(1) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group

(e.g., phenyl), a C₆₋₁₄ aryloxy group (e.g., phenoxy) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl) or (3) -NR²R³ [R² is a hydrogen atom, and R³ is a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (b) a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl)].

[0103] Ring A is an optionally further substituted aromatic ring.

[0104] Examples of the "aromatic ring" of the "optionally further substituted aromatic ring" for ring A include a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring), and a 5- to 14-membered aromatic heterocycle (e.g., pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring).

[0105] The "aromatic ring" of the "optionally further substituted aromatic ring" for ring A is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents at substitutable position(s). Examples of such substituent include the above-mentioned "substituent".

[0106] In one embodiment of the present invention, the "aromatic ring" of the "optionally further substituted aromatic ring" for ring A is preferably further substituted by a substituent at the 3-position or the 4-position with the position bonded to the nitrogen atom substituted by R¹CO as the 1-position.

[0107] The substituent of the "aromatic ring" of the "optionally further substituted aromatic ring" for ring A is preferably (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl), (5) an optionally substituted C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (7) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyran, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) or (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl).

[0108] The substituent of the "aromatic ring" of the "optionally further substituted aromatic ring" for ring A is more preferably,

(1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 3- to 14-membered non-aromatic heterocyclic group (e.g., piperazinyl, piperidinyl, morpholinyl) optionally substituted 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (5) a C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a cyano group, (c) a C₁₋₆ alkoxy group (e.g., methoxy) and (d) a carbamoyl group, (7) a C₁₋₆ alkoxy group (e.g., methoxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., ethyl) optionally substituted by 1 to 3 C₁₋₆ alkoxy groups (e.g., methoxy), (b) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a cyano group and a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (9) a carboxy group, (10) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (11) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl), (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) a C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl), (f) a carbamoyl group, (g) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino) and (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyran, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) or (12) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a C₁₋₆ alkoxy group (e.g., methoxy), a carbamoyl group, a 3- to 14-membered non-aromatic heterocyclic group (e.g., morpholinyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (c) a C₁₋₆ alkoxy group (e.g., methoxy), (d) an amino group, (e) a carboxy group, (f) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl), (g) a carbamoyl group and (h) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyran).

[0109] The substituent of the "aromatic ring" of the "optionally further substituted aromatic ring" for ring A is further preferably,

a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl) and (c) a C₁₋₆ alkoxy group (e.g., methoxy).

[0110] Ring A is preferably

a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl), (5) an optionally substituted C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (7) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl).

[0111] Ring A is more preferably,

a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 3- to 14-membered non-aromatic heterocyclic group (e.g., piperazinyl, piperidinyl, morpholinyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (5) a C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a cyano group, (c) a C₁₋₆ alkoxy group (e.g., methoxy) and (d) a carbamoyl group, (7) a C₁₋₆ alkoxy group (e.g., methoxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., ethyl) optionally substituted by 1 to 3 C₁₋₆ alkoxy groups (e.g., methoxy), (b) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a cyano group and a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (9) a carboxy group, (10) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (11) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl), (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (f) a carbamoyl group, (g) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino) and (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (12) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a C₁₋₆ alkoxy group (e.g., methoxy), a carbamoyl group, a 3- to 14-membered non-aromatic heterocyclic group (e.g., morpholinyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (c) a C₁₋₆ alkoxy group (e.g., methoxy), (d) an amino group, (e) a carboxy group, (f) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl), (g) a carbamoyl group and (h) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl).

[0112] Ring A is further preferably,

a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., a pyridine ring, a pyrimidine ring, a pyridazine ring, a pyrazine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkoxy group (e.g., methoxy).

[0113] Ring B is an optionally further substituted cyclohexane ring.

[0114] The "cyclohexane ring" of the "optionally further substituted cyclohexane ring" for ring B is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents at substitutable position(s). Examples of such substituent include the above-mentioned "substituent".

[0115] Ring B is preferably a cyclohexane ring not substituted further.

[0116] X is CH or N, and ring C is an optionally further substituted 6-membered nitrogen-containing aromatic heterocycle.

[0117] The "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is a pyridine ring (that is, X is CH), or a pyrimidine ring (that is, X is N).

[0118] The "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents

at substitutable position(s) (when X is CH, the CH is unsubstituted). Examples of such substituent include the above-mentioned "substituent".

[0119] In one embodiment of the present invention, the "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is preferably further substituted by substituent(s) at the 4-position and/or the 5-position, further preferably at both the 4-position and the 5-position.

[0120] The substituent of the "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is preferably

(1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group (e.g., methyl), (4) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (5) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (6) an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperaziny, piperidiny, morpholiny, azepany, thiazepany, pyrrolidiny, oxazepany, diazepany, thiomorpholiny, imidazolidiny, dihydroimidazopyraziny, dihydrothiazolopyridyl, dihydrotriazolopyraziny, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxaziny, dihydroindolyl, dihydrotriazolopyraziny, oxazolidiny, dihydropyrrolopyridyl, thiadianyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, aza-spiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxaza-spiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) or (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridaziny, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl).

[0121] The substituent of the "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is more preferably

(1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (4) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom, chlorine atom), (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (e) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (f) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (g) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group (e.g., morpholiny-sulfonyl), (5) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom) and (b) a 5- to 14-membered aromatic heterocyclic group (e.g., oxazolyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., tert-butyl), (6) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, neopentyl, 1,2-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (vii) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (viii) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), (xi) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, thietanyl, morpholiny, pyrrolidiny, tetrahydrofuryl, tetrahydropyrany) optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group (e.g., methyl) and (xii) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridaziny, pyraziny, oxadiazolyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, tert-butyl), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a (C₁₋₆ alkyl) (C₁₋₆ alkylsulfonyl) amino group (e.g., N-methylsulfonyl-N-methylamino), (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups (e.g., methyl) and a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, spiro [2.2]pentyl), (c) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (d) a C₃₋₁₀ cycloalkylcarbonyl group (e.g., cyclopropylcarbonyl),

(e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and C₁₋₆ alkyl group (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, tetrahydrofuryl, dihydroindolyl, tetrahydropyranyl, oxabicyclo[2.2.1]heptyl, azaspiro[2.4]heptyl, oxabicyclo[4.2.0]octyl) and (f) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl), (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom (e.g., fluorine atom), (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group and a C₁₋₆ alkoxy group (e.g., methoxy), (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (h) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-ethylamino), (l) a dimethyl(oxide)-λ⁶-sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperaziny, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthiridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadiazinyl, hexahydropyrrolopyrrolidyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) or (11) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom (e.g., chlorine atom), (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₆₋₁₄ aryl group (e.g., phenyl), a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl) and a carbamoyl group, (f) a C₁₋₆ alkoxy group (e.g., methoxy), (g) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl), (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and (i) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl).

[0122] The substituent of the "6-membered nitrogen-containing aromatic heterocycle" of the "optionally further substituted 6-membered nitrogen-containing aromatic heterocycle" for ring C is further preferably,

(1) a cyano group, (2) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (3) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (4) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., n-propyl) optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group and (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, azepanyl, oxazaspiro[3.4]octyl) or (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen atom (e.g., chlorine atom), (c) a C₁₋₆ alkyl group (e.g., methyl) and (d) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl).

[0123] Ring C is preferably

a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N), each of which is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group (e.g., methyl), (4) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (5) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (6) an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperaziny, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthiridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thia-

dianyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl).

[0124] Ring C is more preferably,

a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N), each of which is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (4) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom, chlorine atom), (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (e) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (f) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylaminol), (g) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group (e.g., morpholinylsulfonyl), (5) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom) and (b) a 5- to 14-membered aromatic heterocyclic group (e.g., oxazolyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., tert-butyl), (6) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, neopentyl, 1,2-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (vii) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (viii) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylaminol), (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), (xi) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, thietanyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group (e.g., methyl) and (xii) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, tert-butyl), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a (C₁₋₆ alkyl) (C₁₋₆ alkylsulfonyl) amino group (e.g., N-methylsulfonyl-N-methylamino) (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups and a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, spiro [2.2]pentyl), (c) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (d) a C₃₋₁₀ cycloalkylcarbonyl group (e.g., cyclopropylcarbonyl), (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and a C₁₋₆ alkyl group (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, tetrahydrofuryl, dihydroindolyl, tetrahydropyranyl, oxabicyclo[2.2.1]heptyl, azaspiro[2.4]heptyl, oxabicyclo[4.2.0]octyl) and (f) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl), (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom (e.g., fluorine atom), (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group and a C₁₋₆ alkoxy group (e.g., methoxy), (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (h) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-ethylamino), (l) a dimethyl (oxide)- λ^6 -sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperazinyl, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadianyl, hexahydropyrrolopyrrolyl, oc-

tetrahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom (e.g., chlorine atom), (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₆₋₁₄ aryl group (e.g., phenyl), a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl) and a carbamoyl group, (f) a C₁₋₆ alkoxy group (e.g., methoxy), (g) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl), (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and (i) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl).

[0125] Ring C is further preferably,

a pyrimidine ring (that is, X is N) optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a cyano group, (2) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (3) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (4) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., n-propyl) optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group and (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidyl, azepanyl, oxazaspiro[3.4]octyl) and (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen atom (e.g., chlorine atom), (c) a C₁₋₆ alkyl group (e.g., methyl) and (d) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl).

[0126] In one preferred embodiment of the present invention, ring C has a substituent other than halogen atom at least at a para-position relative to the bonding position of group: -NH-ring B-N(C(=O)R¹)-ring A. As such substituent, preferable substituents (excluding halogen atom) of ring C mentioned above can be recited.

[0127] Preferable examples of compound (I) include the following compounds.

[Compound I-1]

[0128] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (4) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), R³ is (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, neopentyl) optionally substituted by 1 to 3 substituents selected from an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl) and an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) or (ii) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl);

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl), (5) an optionally substituted C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (7) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-

membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N), each of which is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group (e.g., methyl), (4) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (5) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (6) an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperazinyl, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadiazinyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, aza-spiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxaza-spiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl).

[Compound I-2]

[0129] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., chlorine atom), a C₆₋₁₄ aryloxy group (e.g., phenoxy) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) a C₆₋₁₄ aryl group (e.g., phenyl), (4) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidiny, tetrahydropyranyl) optionally substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl) or (5) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl), R³ is (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, neopentyl) optionally substituted by 1 to 3 substituents selected from (a) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), (b) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a cyano group, a C₁₋₆ alkoxy group (e.g., methoxy), a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino), (c) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl) and (d) a 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl) and a C₁₋₆ alkoxy group (e.g., methoxy) or (ii) a C₆₋₁₄ aryl group (e.g., phenyl)];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 3- to 14-membered non-aromatic heterocyclic group (e.g., piperazinyl, piperidinyl, morpholinyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (5) a C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a cyano group, (c) a C₁₋₆ alkoxy group (e.g., methoxy) and (d) a carbamoyl group, (7) a C₁₋₆ alkoxy group (e.g., methoxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., ethyl) optionally substituted by 1 to 3 C₁₋₆ alkoxy groups (e.g., methoxy), (b) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a cyano group and a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (9) a carboxy group, (10) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (11) a 3- to

14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl), (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (f) a carbamoyl group, (g) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino) and (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (12) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a C₁₋₆ alkoxy group (e.g., methoxy), a carbamoyl group, a 3- to 14-membered non-aromatic heterocyclic group (e.g., morpholinyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (c) a C₁₋₆ alkoxy group (e.g., methoxy), (d) an amino group, (e) a carboxy group, (f) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl), (g) a carbamoyl group and (h) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N), each of which is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (4) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom, chlorine atom), (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (e) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (f) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (g) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group (e.g., morpholinylsulfonyl), (5) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom) and (b) a 5- to 14-membered aromatic heterocyclic group (e.g., oxazolyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., tert-butyl), (6) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, neopentyl, 1,2-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (vii) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (viii) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), (xi) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, thietanyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group (e.g., methyl) and (xii) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, tert-butyl), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a (C₁₋₆ alkyl) (C₁₋₆ alkylsulfonyl) amino group (e.g., N-methylsulfonyl-N-methylamino), (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups and a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, spiro[2.2]pentyl), (c) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (d) a C₃₋₁₀ cycloalkylcarbonyl group (e.g., cyclopropylcarbonyl), (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and a C₁₋₆ alkyl group (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, tetrahydrofuryl, dihydroindolyl, tetrahydropyranyl, oxabicyclo[2.2.1]heptyl, azaspiro[2.4]heptyl, oxabicyclo[4.2.0]octyl) and (f) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl), (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom (e.g., fluorine atom), (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group and a C₁₋₆ alkoxy group (e.g., methoxy), (f) a C₃₋₁₀

cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (h) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-ethylamino), (l) a dimethyl (oxide)-λ⁶-sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperaziny, piperidiny, morpholiny, azepany, thiazepany, pyrrolidiny, oxazepany, diazepany, thiomorpholiny, imidazolidiny, dihydroimidazopyraziny, dihydrothiazolopyridyl, dihydrotriazolopyraziny, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxaziny, dihydroindolyl, dihydrotriazolopyraziny, oxazolidiny, dihydropyrrolopyridyl, thiadianyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridaziny, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom (e.g., chlorine atom), (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₆₋₁₄ aryl group (e.g., phenyl), a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl) and a carbamoyl group, (f) a C₁₋₆ alkoxy group (e.g., methoxy), (g) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl), (h) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and (i) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyrany).

[Compound I-3]

[0130] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl), a C₆₋₁₄ aryloxy group (e.g., phenoxy) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (2) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from a C₆₋₁₄ aryl group (e.g., phenyl) and a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), or (3) - NR²R³ [R² is a hydrogen atom, R³ is a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (b) a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl);

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., a pyridine ring, a pyrimidine ring, a pyridazine ring, a pyrazine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkoxy group (e.g., methoxy);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a cyano group, (2) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (3) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (4) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., n-propyl) optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group and (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, azepany, oxazaspiro[3.4]octyl) and (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen atom (e.g., chlorine atom), (c) a C₁₋₆ alkyl group (e.g., methyl) and (d) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl).

[Compound I-4]

[0131] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), optionally substituted C₃₋₁₀ cycloalkyl

group (e.g., cyclopropyl), optionally substituted C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) and optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), (2) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), optionally substituted amino group, optionally substituted 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, morpholinyl) and optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (4) 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, pyrrolidinyl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, optionally substituted C₁₋₆ alkyl group (e.g., methyl), optionally substituted C₁₋₆ alkoxy group (e.g., methoxy) and optionally substituted C₆₋₁₄ aryl group (e.g., phenyl) or (5)-NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), R³, (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, isobutyl, neopentyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), optionally substituted amino group, optionally substituted 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydropyranyl) and optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl), (ii) optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl) or (iii) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl)];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyrazole ring, pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a cyano group, (3) a hydroxy group, (4) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl), (5) an optionally substituted C₂₋₆ alkenyl group (e.g., ethenyl, 2-propenyl), (6) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (7) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy, ethoxy), (8) an optionally substituted amino group, (9) a carboxy group, (10) an optionally substituted carbamoyl group, (11) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyridine ring (that is, X is CH) or a pyrimidine ring (that is, X is N), each of which is optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) an optionally substituted C₁₋₆ alkyl group (e.g., methyl), (4) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), (5) an optionally substituted C₁₋₆ alkoxy group (e.g., methoxy), (6) an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy), (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy), (8) an optionally substituted amino group, (9) an optionally substituted carbamoyl group, (10) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidyl, piperazinyl, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydropyranyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydroimidazopyrazinyl, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadiazinyl, tetrahydronaphthyridinyl, tetrahydroimidazopyrazinyl, hexahydropyrrolopyrrololyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) an optionally substituted 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl).

[Compound I-5]

[0132] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g.,

cyclopropyl), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) and a C₆₋₁₄ aryloxy group (e.g., phenoxy), (2) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom) and an amino group, (d) a C₆₋₁₄ aryl group (e.g., phenyl), (e) a C₁₋₆ alkoxy group (e.g., methoxy), (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (g) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidiny, morpholinyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (h) a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (3) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidiny, pyrrolidinyl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group (e.g., methyl), a C₁₋₆ alkoxy group (e.g., methoxy) and a C₆₋₁₄ aryl group (e.g., phenyl) or (4) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl), and R³ is (i) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, isobutyl, neopentyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom) and an amino group, (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (g) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydropyranyl) and (h) a 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) or (ii) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom)];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyrazole ring, pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom) and (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (3) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (4) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by a C₁₋₆ alkoxy group (e.g., methoxy), (5) a 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxazaspiro[3.5]nonyl) and (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a 3- to 14-membered non-aromatic heterocyclic group (e.g., morpholinyl), (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) an amino group, (f) a carboxy group, (g) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and (h) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (4) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom, chlorine atom), (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (e) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (f) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (g) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group (e.g., morpholinylsulfonyl), (5) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., oxazolyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., tert-butyl), (6) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, neopentyl, 1,2-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a hydroxy

group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (vii) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (viii) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), (xi) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, thietanyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group (e.g., methyl) and (xii) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, tert-butyl), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a (C₁₋₆ alkyl) (C₁₋₆ alkylsulfonyl) amino group (e.g., N-methylsulfonyl-N-methylamino), (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups (e.g., methyl) and a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, spiro [2.2]pentyl), (c) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (d) a C₃₋₁₀ cycloalkylcarbonyl group (e.g., cyclopropylcarbonyl), (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and C₁₋₆ alkyl group (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, tetrahydrofuryl, dihydroindolyl, tetrahydropyranyl, oxabicyclo[2.2.1]heptyl, azaspiro[2.4]heptyl, oxabicyclo[4.2.0]octyl) and (f) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl), (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom (e.g., fluorine atom), (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group and a C₁₋₆ alkoxy group (e.g., methoxy), (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (h) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-ethylamino), (l) a dimethyl(oxide)-λ⁶-sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidyl, piperaziny, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydropyranyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadianyl, tetrahydronaphthyridinyl, tetrahydroimidazopyrazinyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₆₋₁₄ aryl group (e.g., phenyl), a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl) and a carbamoyl group, (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy), (h) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl), (i) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and (j) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl).

[Compound I-6]

[0133] Compound (I) wherein R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a C₁₋₆ alkoxy group (e.g., ethoxy) and a C₆₋₁₄ aryloxy group (e.g., phenoxy), (2) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₆₋₁₄ aryl group (e.g., phenyl), (d) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl) and (e) a 5- to 14-membered

aromatic heterocyclic group (e.g., pyridyl) or (3) -NR²R³ [R² is a hydrogen atom, and R³ is a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isobutyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (e) a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl)];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., a pyridine ring, a pyrimidine ring, a pyridazine ring, a pyrazine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl, pyridyl, pyrimidinyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkoxy group (e.g., methoxy);

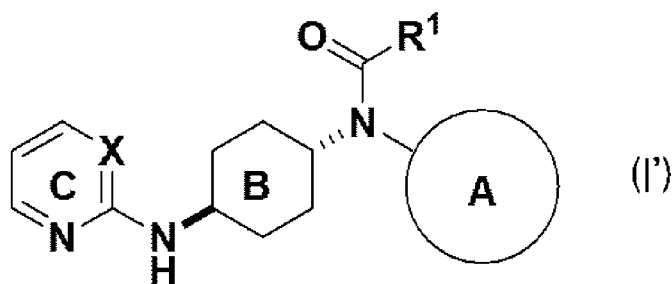
ring B is a cyclohexane ring not substituted further; and

ring C is a pyrimidine ring (that is, X is N) optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a cyano group, (2) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (3) a 3- to 14-membered non-aromatic heterocyclic-oxo group (e.g., oxetanyloxy), (4) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., n-propyl) optionally substituted by 1 to 3 hydroxy groups and (b) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl), (5) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group and (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 hydroxy groups (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidyl, azepanyl, oxazaspiro[3.4]octyl) and (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from (a) a cyano group, (b) a halogen atom (e.g., chlorine atom), (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (d) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl).

[0134] Specific examples of compound (I) include, for example, the compounds of Examples 1 - 19, 21 - 187, 191 - 483, 485 - 633 and 634 - 858.

[0135] The present invention also encompasses the following compounds.

[0136] A compound represented by the formula (I'):



wherein

X is N;

R¹ is an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₃₋₁₀ cycloalkyloxy group, an optionally substituted C₆₋₁₄ aryl group, an optionally substituted heterocyclic group, or -NR²R³;

R² is a hydrogen atom or a substituent;

R³ is a hydrogen atom or a substituent;

ring A is an optionally further substituted aromatic ring;

ring B is an optionally further substituted cyclohexane ring; and

ring C is an optionally further substituted 6-membered nitrogen-containing aromatic heterocycle, or a salt thereof (sometimes to be abbreviated as "compound (I')" in the present specification).

[0137] Preferable examples of compound (I') include the following compounds.

[Compound I'-1]

[0138] Compound (I') wherein X is N;

R¹ is (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) and a C₆₋₁₄ aryloxy group (e.g., phenoxy), (2) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (3) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom) and an amino group, (d) a C₆₋₁₄ aryl group (e.g., phenyl), (e) a C₁₋₆ alkoxy group (e.g., methoxy), (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (g) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, morpholinyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and (h) a 5- to 14-membered aromatic heterocyclic group (e.g., pyridyl), (4) a C₃₋₁₀ cycloalkyloxy group (e.g., cyclopropyloxy, cyclobutyloxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (5) a 3- to 14-membered non-aromatic heterocyclic group (e.g., azetidyl, pyrrolidinyl, tetrahydropyranyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group (e.g., methyl), a C₁₋₆ alkoxy group (e.g., methoxy) and a C₆₋₁₄ aryl group (e.g., phenyl) or (6) -NR²R³ [R² is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl), and R³ is (i) a hydrogen atom, (ii) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, isobutyl, neopentyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a hydroxy group, (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom) and an amino group, (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (f) an amino group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (g) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydropyranyl) and (h) a 5- to 14-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, pyridyl, pyrimidinyl) or (iii) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom)];

ring A is a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene ring) or a 5- to 14-membered aromatic heterocycle (e.g., pyrazole ring, pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, indazole ring, pyrazolopyridine ring), each of which is optionally further substituted by 1 - 5 (preferably 1 - 3, more preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom), (2) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom) and (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (3) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a C₁₋₆ alkoxy group (e.g., methoxy) and (c) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl), (4) a carbamoyl group optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by a C₁₋₆ alkoxy group (e.g., methoxy), (5) a 3- to 14-membered non-aromatic heterocyclic group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a spiro ring structure; for example, piperazinyl, piperidinyl, morpholinyl, dihydropyranyl, tetrahydropyridyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyrazolopyridyl, oxaza-spiro[3.5]nonyl) and (6) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, thiazolyl, furyl, oxazolyl, pyridyl, pyrimidinyl, pyrazinyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl, isobutyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a 3- to 14-membered non-aromatic heterocyclic group (e.g., morpholinyl), (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (d) a C₁₋₆ alkoxy group (e.g., methoxy), (e) an amino group, (f) a carboxy group, (g) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and (h) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranyl);

ring B is a cyclohexane ring not substituted further; and

ring C is a pyrimidine ring optionally further substituted by 1 - 3 (preferably 1 - 2) substituents selected from (1) a halogen atom (e.g., fluorine atom, chlorine atom), (2) a cyano group, (3) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (4) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom, chlorine atom), (b) a cyano group, (c) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (d) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (e) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (f) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (g) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (h) a carbamoyl group, (i) a sulfamoyl group and (j) a 3- to 14-membered non-aromatic heterocyclic-sulfonyl group (e.g., morpholinylsulfonyl), (5) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 substituents selected from (a) a halogen atom (e.g., fluorine atom), (b) a 3- to 14-membered

non-aromatic heterocyclic group (e.g., oxetanyl) and (c) a 5- to 14-membered aromatic heterocyclic group (e.g., oxazolyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., tert-butyl), (6) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (7) a 3- to 14-membered non-aromatic heterocyclic-oxy group (e.g., oxetanyloxy) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), (8) an amino group optionally mono- or di-substituted by substituent(s) selected from (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, neopentyl, 1,2-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a hydroxy group, (iii) a cyano group, (iv) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally substituted by 1 to 3 hydroxy groups, (v) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and a sulfamoyl group, (vi) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (vii) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), (viii) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino), (ix) a carbamoyl group, (x) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), (xi) a 3- to 14-membered non-aromatic heterocyclic group (e.g., oxetanyl, thietanyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydropyranlyl) optionally substituted by 1 to 3 substituents selected from an oxo group and a C₁₋₆ alkyl group (e.g., methyl) and (xii) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, tert-butyl), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) and a (C₁₋₆ alkyl) (C₁₋₆ alkylsulfonyl) amino group (e.g., N-methylsulfonyl-N-methylamino), (b) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group, a C₁₋₆ alkyl group optionally substituted by 1 to 3 hydroxy groups (e.g., methyl) and a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) (the C₃₋₁₀ cycloalkyl group also includes one having a spiro ring structure; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, spiro[2.2]pentyl), (c) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, isopropylsulfonyl), (d) a C₃₋₁₀ cycloalkylcarbonyl group (e.g., cyclopropylcarbonyl), (e) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from an oxo group, a hydroxy group and C₁₋₆ alkyl group (e.g., methyl) (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrothiopyranlyl, tetrahydrofuryl, dihydroindolyl, tetrahydropyranlyl, oxabicyclo[2.2.1]heptyl, azaspiro[2.4]heptyl, oxabicyclo[4.2.0]octyl) and (f) a 5- to 14-membered aromatic heterocyclic group (e.g., pyrazolyl), (9) a carbamoyl group, (10) a 3- to 14-membered non-aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a halogen atom (e.g., fluorine atom), (c) a hydroxy group, (d) a cyano group, (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a hydroxy group and a C₁₋₆ alkoxy group (e.g., methoxy), (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (h) a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl), (i) a carbamoyl group, (j) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), (k) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-ethylamino), (l) a dimethyl(oxide)-λ⁶-sulfanylideneamino group and (m) a methylimino group (the 3- to 14-membered non-aromatic heterocyclic group also includes one having a bicyclo ring structure, a bridged ring structure, or a spiro ring structure; for example, azetidiny, piperazinyl, piperidinyl, morpholinyl, azepanyl, thiazepanyl, pyrrolidinyl, oxazepanyl, diazepanyl, thiomorpholinyl, imidazolidinyl, dihydropyranlyl, dihydroimidazopyrazinyl, dihydrothiazolopyridyl, dihydrotriazolopyrazinyl, dihydrobenzimidazolyl, dihydronaphthyridyl, dihydroquinazolyl, dihydropyridoxazinyl, dihydroindolyl, dihydrotriazolopyrazinyl, oxazolidinyl, dihydropyrrolopyridyl, thiadianyl, tetrahydronaphthyridinyl, tetrahydroimidazopyrazinyl, hexahydropyrrolopyrrolyl, octahydropyrrolopyridyl, azabicyclo[3.2.1]octyl, azabicyclo[3.1.0]hexyl, oxazaspiro[3.5]nonyl, diazaspiro[4.5]decyl, diazaspiro[3.5]nonyl, oxazaspiro[5.5]undecyl, oxazaspiro[4.5]decyl, diazaspiro[4.4]nonyl, diazaspiro[3.4]octyl, azaspiro[2.4]heptyl, oxazaspiro[3.4]octyl, thiazaspiro[4.5]decyl, oxazaspiro[4.4]nonyl, oxazaspiro[3.3]heptyl, dioxazaspiro[3.5]nonyl, oxadiazaspiro[4.5]decenyl, oxadiazaspiro[4.6]undecenyl, oxadiazaspiro[3.4]octyl, oxadiazaspiro[4.4]nonenyl, oxadiazaspiro[3.4]octenyl) and (11) a 5- to 14-membered aromatic heterocyclic group (e.g., thienyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, indolyl, pyrazolopyridyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazopyridyl, benzoxadiazolyl) optionally substituted by 1 to 3 substituents selected from (a) an oxo group, (b) a hydroxy group, (c) a cyano group, (d) a halogen atom (e.g., chlorine atom, bromine atom), (e) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a hydroxy group, a halogen atom (e.g., fluorine atom), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), a C₆₋₁₄ aryl group (e.g., phenyl), a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl) and a carbamoyl group, (f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), (g) a C₁₋₆ alkoxy group (e.g., methoxy), (h) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl), (i) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and (j) a 3- to 14-membered non-aromatic heterocyclic group (e.g., tetrahydropyranlyl).

[0139] As a salt of a compound represented by the formula (I), a pharmacologically acceptable salt is preferable, and examples of such salt include a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, and a salt with basic or acidic amino acid.

[0140] Preferable examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like, alkaline earth metal salts such as calcium salt, magnesium salt and the like, aluminum salt, and ammonium salt.

[0141] Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, tromethamine [tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, and N,N-dibenzylethylenediamine.

[0142] Preferable examples of the salt with inorganic acid include salts with hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, and phosphoric acid.

[0143] Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid.

[0144] Preferable examples of the salt with basic amino acid include salts with arginine, lysine, and ornithine.

[0145] Preferable examples of the salt with acidic amino acid include salts with aspartic acid, and glutamic acid.

[0146] The production method of the compound of the present invention is explained in the following.

[0147] The starting materials and reagents used in each step in the following production method, and the obtained compounds each may form a salt. Examples of the salt include those similar to the aforementioned salts of the compound of the present invention and the like.

[0148] When the compound obtained in each step is a free compound, it can be converted to a desired salt by a method known per se. Conversely, when the compound obtained in each step is a salt, it can be converted to a free form or a desired other kind of salt by a method known per se.

[0149] The compound obtained in each step can also be used for the next reaction as a reaction mixture thereof or after obtaining a crude product thereof. Alternatively, the compound obtained in each step can be isolated and/or purified from the reaction mixture by a separation means such as concentration, crystallization, recrystallization, distillation, solvent extraction, fractionation, chromatography and the like according to a conventional method.

[0150] When the starting materials and reagent compounds of each step are commercially available, the commercially available products can be used as they are.

[0151] In the reaction of each step, while the reaction time varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally 1 min - 48 hr, preferably 10 min - 8 hr.

[0152] In the reaction of each step, while the reaction temperature varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally -78°C to 300°C, preferably -78°C to 150°C.

[0153] In the reaction of each step, while the pressure varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally 1 atm - 20 atm, preferably 1 atm - 3 atm.

[0154] In the reaction of each step, for example, microwave synthesizers such as Initiator manufactured by Biotage and the like are sometimes used. While the reaction temperature varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally room temperature - 300°C, preferably 50°C - 250°C. While the reaction time varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally 1 min - 48 hr, preferably 1 min - 8 hr.

[0155] In the reaction of each step, unless otherwise specified, a reagent is used in 0.5 equivalent - 20 equivalents, preferably 0.8 equivalent - 5 equivalents, relative to the substrate. When a reagent is used as a catalyst, the reagent is used in 0.001 equivalent - 1 equivalent, preferably 0.01 equivalent - 0.2 equivalent, relative to the substrate. When the reagent is also a reaction solvent, the reagent is used in a solvent amount.

[0156] In the reaction of each step, unless otherwise specified, it is performed without solvent or by dissolving or suspending in a suitable solvent. Specific examples of the solvent include those described in Examples and the following. alcohols: methanol, ethanol, tert-butyl alcohol, 2-methoxyethanol and the like;

ethers: diethyl ether, diphenyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; aromatic hydrocarbons: chlorobenzene, toluene, xylene and the like;

saturated hydrocarbons: cyclohexane, hexane and the like; amides: N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like;

halogenated hydrocarbons: dichloromethane, carbon tetrachloride and the like;

nitriles: acetonitrile and the like;

sulfoxides: dimethyl sulfoxide and the like;

aromatic organic bases: pyridine and the like;

acid anhydrides: acetic anhydride and the like;

organic acids: formic acid, acetic acid, trifluoroacetic acid and the like;

inorganic acids: hydrochloric acid, sulfuric acid and the like; esters: ethyl acetate and the like;
ketones: acetone, methyl ethyl ketone and the like; and water.

[0157] Two or more kinds of the above-mentioned solvents may be used by mixing at an appropriate ratio.

[0158] When a base is used in the reaction of each step, for example, bases shown below or those described in Examples are used.

inorganic bases: sodium hydroxide, magnesium hydroxide, sodium carbonate, calcium carbonate, sodium hydrogen carbonate and the like;

organic bases: triethylamine, diethylamine, pyridine, 4-dimethylaminopyridine, N,N-dimethylaniline, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene, imidazole, piperidine and the like;

metal alkoxides: sodium ethoxide, potassium tert-butoxide and the like;

alkali metal hydrides: sodium hydride and the like;

metal amides: sodium amide, lithium diisopropyl amide, lithium hexamethyl disilazide and the like; and

organic lithiums: n-butyllithium and the like.

[0159] When an acid or acidic catalyst is used in the reaction of each step, for example, acids and acidic catalysts shown below or those described in Examples are used.

inorganic acids: hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid and the like;

organic acids: acetic acid, trifluoroacetic acid, citric acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and the like; and

Lewis acids: boron trifluoride diethyl ether complex, zinc iodide, anhydrous aluminum chloride, anhydrous zinc chloride, anhydrous iron chloride and the like.

[0160] Unless otherwise specified, the reaction of each step is performed according to a method known per se, for example, the methods described in Jikken Kagaku Kouza 5th edition, vol. 13 - vol. 19 (The Chemical Society of Japan ed.); Shinjikken Kagaku Kouza (Courses in Experimental Chemistry), vol. 14 - vol. 15 (The Chemical Society of Japan ed.); Fine Organic Chemistry rev. 2nd edition (L. F. Fieser, Th. Eicher, NANKODO); rev. Organic Name Reactions, Their Mechanism and Essence (Hideo Togo, Kodansha); ORGANIC SYNTHESIS Collective Volume I - VII (John Wiley & Sons Inc); Modern Organic Synthesis in the Laboratory, A Collection of Standard Experimental Procedures (Jie Jack Li, OXFORD UNIVERSITY); Comprehensive Heterocyclic Chemistry III, Vol. 1 - Vol. 14 (Elsevier Japan KK); Strategic Applications of Named Reactions in Organic Synthesis (translation supervisor Kiyoshi Tomioka, KAGAKUDOJIN); Comprehensive Organic Transformations (VCH Publishers Inc.), 1989 and the like, or the methods described in the Examples.

[0161] In each step, protection or deprotection reaction of a functional group is performed by the method known per se, for example, the methods described in "Protective Groups in Organic Synthesis, 4th Ed." (Theodora W. Greene, Peter G. M. Wuts) Wiley-Interscience, 2007; "Protecting Groups 3rd Ed." (P. J. Kocienski) Thieme, 2004 and the like, or the methods described in the Examples.

[0162] Examples of the protecting group of the hydroxyl group of alcohol and the like and a phenolic hydroxyl group include ether protecting groups such as methoxymethyl ether, benzyl ether, tert-butyldimethylsilyl ether, tetrahydropyranyl ether and the like; carboxylate ester protecting groups such as acetate ester and the like; sulfonate ester protecting groups such as methanesulfonate ester and the like; carbonate ester protecting groups such as tert-butylcarbonate and the like, and the like.

[0163] Examples of the protecting group of the carbonyl group of aldehyde include acetal protecting groups such as dimethyl acetal and the like; cyclic acetal protecting groups such as 1,3-dioxane and the like, and the like.

[0164] Examples of the protecting group of the carbonyl group of ketone include ketal protecting groups such as dimethyl ketal and the like; cyclic ketal protecting groups such as 1,3-dioxane and the like; oxime protecting groups such as O-methyloxime and the like; hydrazone protecting groups such as N,N-dimethylhydrazone and the like, and the like.

[0165] Examples of the carboxyl protecting group include ester protecting groups such as methyl ester and the like; amide protecting groups such as N,N-dimethylamide and the like, and the like.

[0166] Examples of the thiol protecting group include ether protecting groups such as benzyl thioether and the like; ester protecting groups such as thioacetate ester, thiocarbonate, thiocarbamate and the like, and the like.

[0167] Examples of the protecting group of an amino group and an aromatic heterocycle such as imidazole, pyrrole, indole and the like include carbamate protecting groups such as benzyl carbamate and the like; amide protecting groups such as acetamide and the like; alkylamine protecting groups such as N-triphenylmethylamine and the like, sulfonamide protecting groups such as methanesulfonamide and the like, and the like.

[0168] The protecting group can be removed by a method known per se, for example, a method using acid, base, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium

acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide), a reduction method and the like.

[0169] When a reduction reaction is performed in each step, examples of the reducing agent to be used include metal hydrides such as lithium aluminum hydride, sodium triacetoxyborohydride, sodium cyanoborohydride, diisobutylaluminum hydride (DIBAL-H), sodium borohydride, tetramethylammonium triacetoxyborohydride and the like; boranes such as borane tetrahydrofuran complex and the like; Raney nickel; Raney cobalt; hydrogen; formic acid; triethylsilane, and the like. When a carbon-carbon double bond or triple bond is reduced, a method using a catalyst such as palladium-carbon, Lindlar catalyst and the like is used.

[0170] When an oxidation reaction is performed in each step, examples of an oxidant to be used include peracids such as m-chloroperbenzoic acid (mCPBA), hydrogen peroxide, tert-butyl hydroperoxide and the like; perchlorates such as tetrabutylammonium perchlorate and the like; chlorates such as sodium chlorate and the like; chlorites such as sodium chlorite and the like; periodic acids such as sodium periodate and the like; high valent iodine reagents such as iodosylbenzene and the like; reagents containing manganese such as manganese dioxide, potassium permanganate and the like; leads such as lead tetraacetate and the like; reagents containing chrome such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Jones reagent and the like; halogen compounds such as N-bromosuccinimide (NBS) and the like; oxygen; ozone; sulfur trioxide pyridine complex; osmium tetroxide; selenium dioxide; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the like.

[0171] When a radical cyclization reaction is performed in each step, examples of the radical initiator to be used include azo compounds such as azobisisobutyronitrile (AIBN) and the like; water-soluble radical initiators such as 4,4'-azobis-4-cyanopentanoic acid (ACPA) and the like; triethylboron in the presence of air or oxygen; benzoyl peroxide and the like. In addition, examples of the radical reaction agent to be used include tributylstannane, tris(trimethylsilyl)silane, 1,1,2,2-tetraphenyldisilane, diphenylsilane, samarium iodide and the like.

[0172] When the Wittig reaction is performed in each step, examples of the Wittig reagent to be used include alkylidenephosphoranes and the like. Alkylidenephosphoranes can be prepared by a method known per se, for example, by reacting a phosphonium salt with a strong base.

[0173] When the Horner-Emmons reaction is performed in each step, examples of the reagent to be used include phosphonoacetic acid esters such as methyl dimethylphosphonoacetate, ethyl diethylphosphonoacetate and the like; and bases such as alkali metal hydrides, organic lithiums and the like.

[0174] When the Friedel-Crafts reaction is performed in each step, examples of the reagent to be used include a combination of Lewis acid and acid chloride, and a combination of Lewis acid and alkylating agent (e.g., alkyl halides, alcohol, olefins and the like). Alternatively, an organic acid and an inorganic acid can also be used instead of the Lewis acid, and acid anhydride such as acetic anhydride and the like can also be used instead of acid chloride.

[0175] When an aromatic nucleophilic substitution reaction is performed in each step, a nucleophilic agent (e.g., amines, imidazole and the like) and a base (e.g., organic bases and the like) are used as the reagent.

[0176] When a nucleophilic addition reaction with carbanion, a nucleophilic 1,4-addition reaction with carbanion (Michael addition reaction) or a nucleophilic substitution reaction with carbanion is performed in each step, examples of the base to be used for developing carbanion include organic lithiums, metal alkoxides, inorganic bases, organic bases and the like.

[0177] When the Grignard reaction is performed in each step, examples of the Grignard reagent include aryl magnesium halides such as phenyl magnesium bromide and the like; and alkyl magnesium halides such as methyl magnesium bromide and the like. The Grignard reagent can be prepared by a method known per se, for example, by reacting alkyl halide or aryl halide with metal magnesium in ether or tetrahydrofuran as a solvent.

[0178] When the Knoevenagel condensation reaction is performed in each step, an active methylene compound held between two electron-withdrawing groups (e.g., malonic acid, diethyl malonate, malononitrile and the like) and a base (e.g., organic bases, metal alkoxides, inorganic bases) are used as the reagents.

[0179] When the Vilsmeier-Haack reaction is performed in each step, phosphoryl chloride and an amide derivative (e.g., N,N-dimethylformamide and the like) are used as the reagents.

[0180] When an azidation reaction of alcohols, alkyl halides or sulfonate esters is performed in each step, examples of the azidation agent to be used include diphenylphosphoryl azide (DPPA), trimethylsilyl azide, sodium azide and the like. For example, when alcohols are azidated, a method using diphenylphosphoryl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a method using trimethylsilyl azide and the Lewis acid and the like can be employed.

[0181] When a reductive amination reaction is performed in each step, examples of the reducing agent to be used include sodium triacetoxyborohydride, sodium cyanoborohydride, hydrogen, formic acid and the like. When the substrate is an amine compound, examples of the carbonyl compound to be used besides para-formaldehyde include aldehydes such as acetaldehyde and the like, ketones such as cyclohexanone and the like. When the substrate is a carbonyl compound, examples of the amines to be used include primary amines such as ammonia, methylamine and the like; secondary amines such as dimethylamine and the like, and the like.

[0182] When the Mitsunobu reaction is performed in each step, azodicarboxylate esters (e.g., diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) and the like) and triphenylphosphine are used as the reagents.

[0183] When an esterification reaction, amidation reaction or ureation reaction is performed in each step, examples of the reagent to be used include halogenated acyl forms such as acid chloride, acid bromide and the like; and activated carboxylic acids such as acid anhydride, active ester form, sulfuric acid ester form and isocyanates. Examples of the carboxylic acid activator include carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride-n-hydrate (DMT-MM) and the like; carbonate ester condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride; lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; a combination thereof and the like. When a carbodiimide condensing agent is used, additives such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like can be further added to the reaction.

[0184] When a coupling reaction is performed in each step, examples of the metal catalyst to be used include palladium compounds such as palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), dichlorobis(triethylphosphine)palladium(II), tris(dibenzylideneacetone)dipalladium(0), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride, palladium(II) acetate and the like; nickel compounds such as tetrakis(triphenylphosphine)nickel(0) and the like; rhodium compounds such as tris(triphenylphosphine)rhodium(III) chloride and the like; a cobalt compound; copper compounds such as copper oxide, copper(I) iodide and the like; a platinum compound and the like. A base may be further added to the reaction and examples of such base include inorganic bases, and the like.

[0185] When a thiocarbonylation reaction is performed in each step, diphosphorus pentasulfide is representatively used as a thiocarbonylating agent. Besides diphosphorus pentasulfide, a reagent having a 1,3,2,4-dithiadiphosphetane-2,4-disulfide structure such as 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson reagent) and the like may also be used.

[0186] When the Wohl-Ziegler reaction is performed in each step, examples of the halogenating agent to be used include N-iodosuccinimide, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), bromine, sulfonyl chloride and the like. Furthermore, the reaction can be accelerated by adding heat, light, radical initiators such as benzoyl peroxide, azobisisobutyronitrile and the like to the reaction.

[0187] When a halogenating reaction of a hydroxy group is performed in each step, examples of the halogenating agent to be used include acid halide of hydrohalic acid and inorganic acid; specifically, hydrochloric acid, thionyl chloride, phosphorus oxychloride and the like for chlorination, and 48% hydrobromic acid and the like for bromination. In addition, a method of obtaining a alkyl halide form from alcohol by reacting with triphenylphosphine and carbon tetrachloride or carbon tetrabromide, and the like may be used. Alternatively, a method of synthesizing a alkyl halide form via a two-step reaction including conversion of alcohol to sulfonic acid ester, and reacting same with lithium bromide, lithium chloride or sodium iodide may also be used.

[0188] When the Arbuzov reaction is performed in each step, examples of the reagent to be used include alkyl halides such as ethyl bromoacetate and the like; and phosphites such as triethyl phosphite, tri(isopropyl) phosphite and the like.

[0189] When a sulfonate esterification reaction is performed in each step, examples of the sulfonylation agent to be used include methanesulfonyl chloride, p-toluenesulfonyl chloride, methanesulfonic anhydride, p-toluenesulfonic anhydride and the like.

[0190] When a hydrolysis reaction is performed in each step, an acid or a base is used as the reagent. In addition, when an acid hydrolysis reaction of tert-butyl ester is performed, formic acid, triethylsilane and the like are sometimes added to reductively trap the by-produced tert-butyl cation.

[0191] When a dehydration reaction is performed in each step, examples of the dehydrating agent to be used include sulfuric acid, phosphorus pentoxide, phosphorus oxychloride, N,N'-dicyclohexylcarbodiimide, alumina, polyphosphoric acid and the like.

[0192] When an acylation reaction is performed in each step, examples of the reagent to be used include halogenated acyl forms such as acid chloride, acid bromide and the like; and activated carboxylic acids such as active ester form, ester form, sulfuric acid ester form and the like. Examples of the carboxylic acid activator include acid anhydride (e.g., acetic anhydride), carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride-n-hydrate (DMT-MM) and the like; carbonate ester condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride; lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; a combination thereof and the like. When a carbodiimide condensing agent is used, additives such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like can be further added to the reaction.

[0193] When a coupling reaction is performed in each step, a ligand may be added in the reaction system. Examples

of the ligand include phosphine ligands [e.g., triphenylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, 2-(di-tert-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl, 2-(dicyclohexylphosphino)-2'-(N,N-dimethylamino)biphenyl, 1,1'-bis(diphenylphosphino)ferrocene, tri-tert-butylphosphine, tricyclohexylphosphine, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene], amine ligands (N,N'-dimethylethylenediamine, trans-1,2-diaminocyclohexane, trans-N,N'-dimethyl-1,2-cyclohexanediamine, 1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline, 3,4,7,8-tetramethyl-1,10-phenanthroline etc.), diketone ligands (2-acetylcyclohexanone, 2-isobutyrylhexanone, 2,2,6,6-tetramethyl-3,5-heptanedione etc.), salicylaldehyde, and proline.

[0194] Examples of the leaving group to be used in each step include a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom), a C₁₋₆ alkoxy group (e.g., methoxy, etc.), a C₆₋₁₄ aryloxy group (e.g., phenoxy, etc.), an optionally substituted acyloxy group (e.g., acetyloxy, benzoyloxy, etc.), an optionally substituted C₁₋₆ alkoxysulfonyloxy group (e.g., methoxysulfonyloxy, etc.), an optionally halogenated C₁₋₆ alkylsulfonyloxy group [e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, trifluoromethanesulfonyloxy(triflate), etc.], an optionally substituted C₆₋₁₄ arylsulfonyloxy group [e.g., C₆₋₁₄ arylsulfonyloxy group optionally having 1 to 3 substituents selected from C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl etc.), C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.) and nitro group, and the like. Specific examples include benzenesulfonyloxy, m-nitrobenzenesulfonyloxy, p-toluenesulfonyloxy, naphthylsulfonyloxy, etc.] and the like.

[0195] When an aromatic nucleophilic substitution reaction is performed in each step, alcohols, thiols and salts thereof can also be used as a nucleophilic agent.

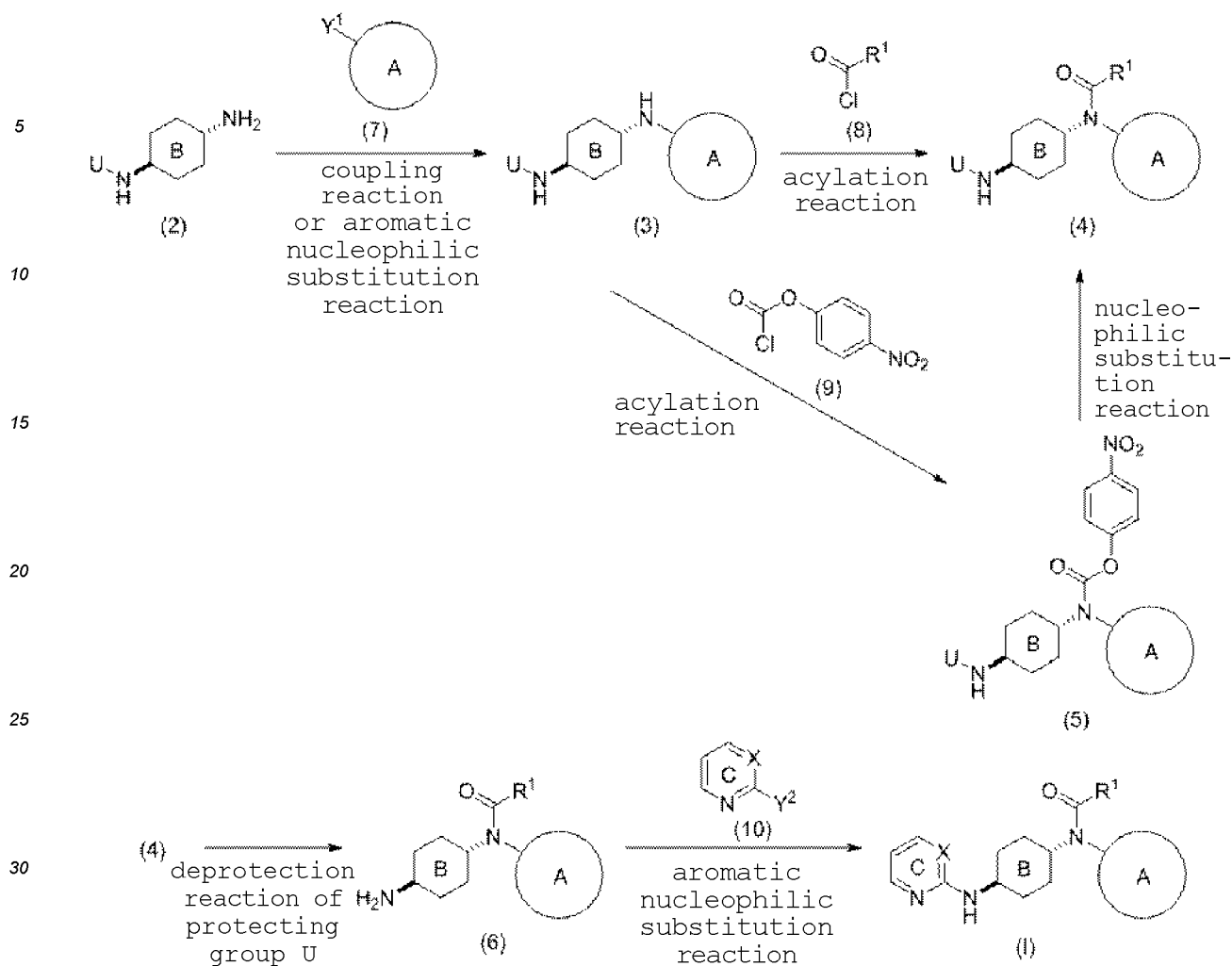
[0196] In the following, the production method of compound (I) is explained.

[0197] Unless otherwise specified, each symbol in the following reaction schemes is as defined above.

[0198] Unless otherwise specified, the starting compounds used in the following various production methods can be produced by methods known per se.

[Production method A-1]

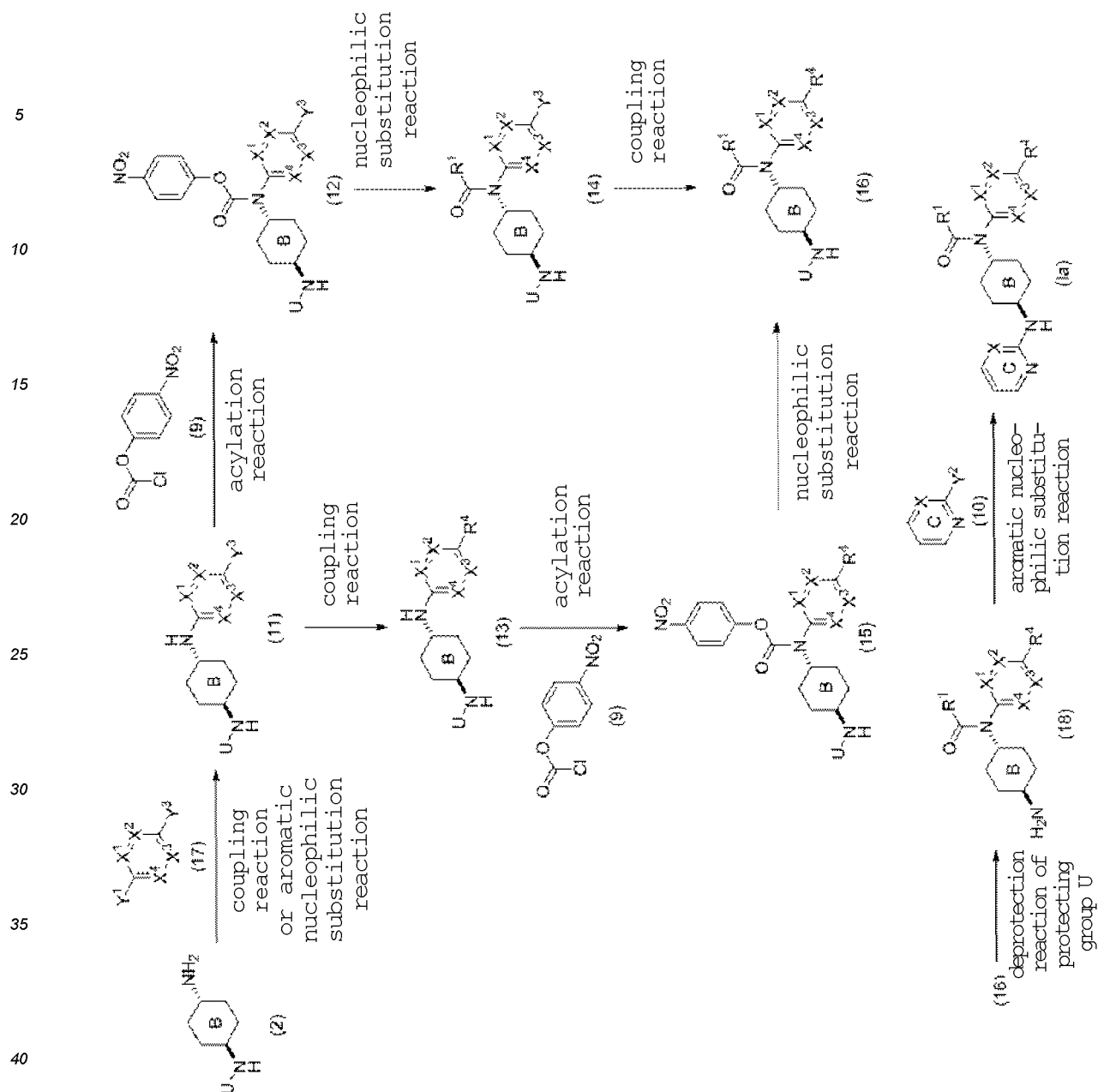
[0199] Compound (I) can be produced from compound (2) by the following method or a method analogous thereto.



wherein Y^1 and Y^2 are the same or different and each is a leaving group, U is an amino-protecting group, and other symbols are as defined above.

[Production method A-2]

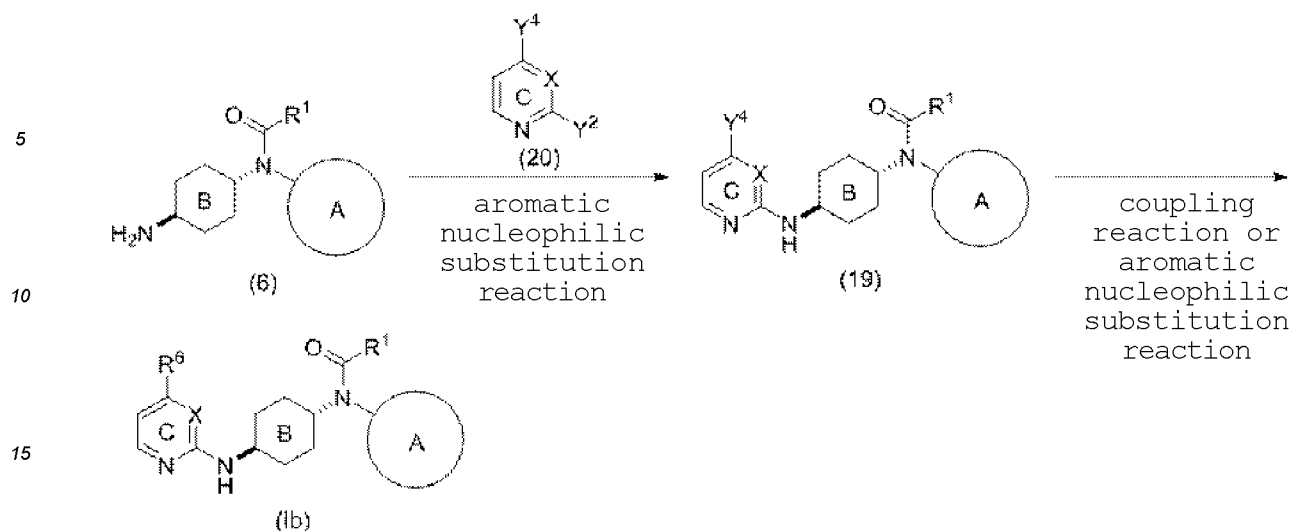
[0200] Compound (Ia) included in compound (I) can be produced from compound (2) by the method shown in the following reaction scheme or a method analogous thereto.



wherein R^4 is an optionally substituted aromatic ring group, X^1 , X^2 , X^3 and X^4 are the same or different CR^5 or a nitrogen atom, R^5 is a hydrogen atom, a halogen atom, or an optionally substituted C_{1-6} alkyl group, Y^3 is a leaving group, and other symbols are as defined above.

[Production method A-3]

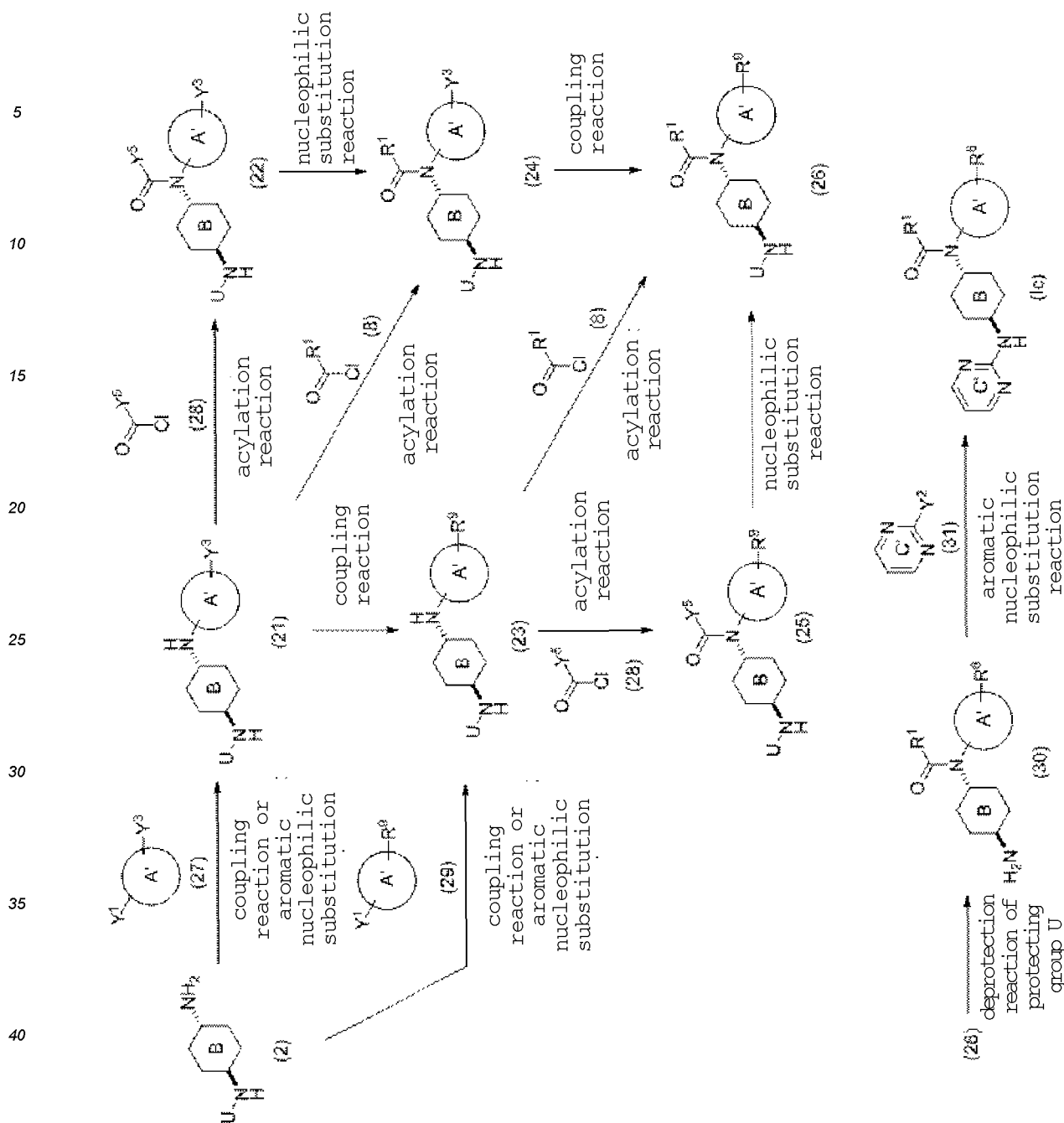
[0201] Compound (1b) included in compound (I) can be produced from compound (6) by the method shown in the following reaction scheme or a method analogous thereto.



wherein R^6 is an optionally substituted aromatic ring group, NR^7R^8 , an optionally substituted C_{1-6} alkoxy group (e.g., methoxy etc.), an optionally substituted C_{3-7} cycloalkoxy group, or an optionally substituted C_{6-14} aryloxy group (e.g., phenoxy etc.), R^7 is a hydrogen atom or a substituent, and R^8 is a substituent. R^7 and R^8 may form a ring. Y^4 is a leaving group, and other symbols are as defined above.

[Production method A-4]

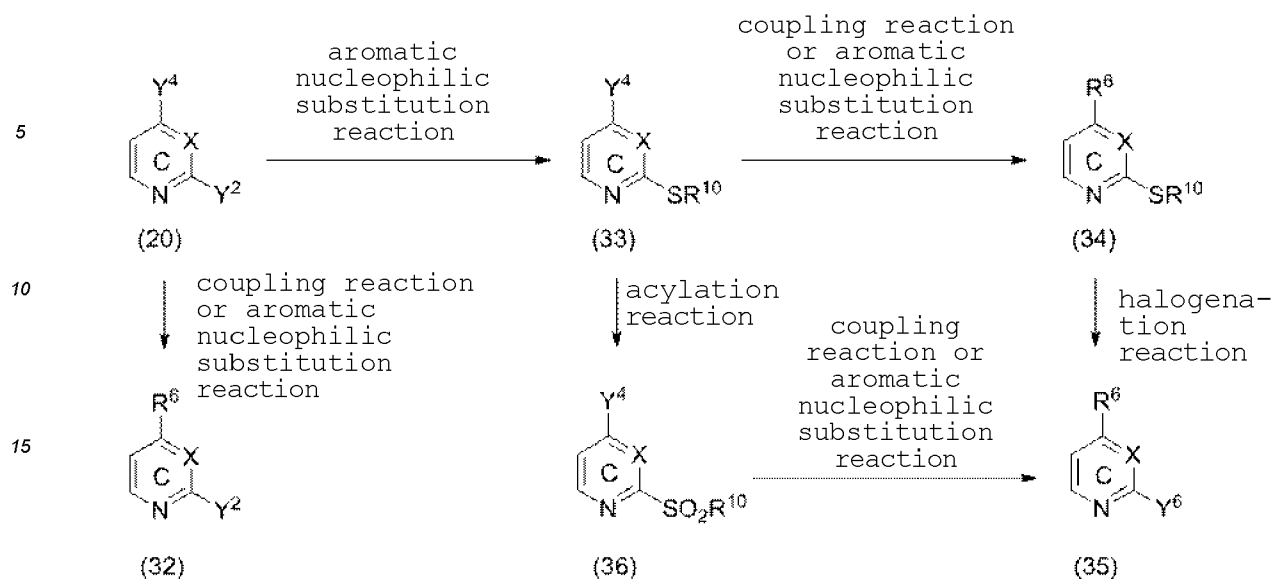
[0202] Compound (1c) included in compound (I) can be produced from compound (2) by the method shown in the following reaction scheme or a method analogous thereto.



wherein A' is an optionally substituted pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, or a pyrazole ring, R⁹ is an optionally substituted aromatic ring group, an alkyl group, an alkoxy group, an alkylaminocarbonyl group or a heterocyclic group, Y⁵ is a leaving group, C' is an optionally substituted pyrimidine ring, and other symbols are as defined above.

[Production method A-5]

[0203] Compounds (32) and (35) included in compound (10) and compound (31) included in the previous reaction can be produced from compound (20) by the method shown in the following reaction scheme or a method analogous thereto.



wherein R^{10} is an alkyl group, Y^6 is a leaving group, and other symbols are as defined above.

[0204] The substituent of the thus-obtained compound (I) is converted (that is, introduction of a substituent or conversion of a functional group) by applying means known per se to produce another compound or a salt thereof encompassed in compound (I).

[0205] As a method for introduction of substituent or conversion of functional group, a known general method is used. For example, conversion of halogen atom (e.g., fluorine, chlorine, bromine, iodine), optionally halogenated C_{1-6} alkylsulfonyloxy group [e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, trifluoromethanesulfonyloxy (triflate)] to methyl group, cyclopropyl group, vinyl group, a cyano group, formyl group, carbonyl group, carboxyl group, hydroxyl group, amino group, boryl group and the like, conversion of formyl group to ethynyl group by Seyferth-Gilbert homologation reaction, conversion of ester to carboxy group by hydrolysis, conversion of carboxy group to carbamoyl group by amidation, conversion of carboxy group to hydroxymethyl group by reduction, conversion of carbonyl group to alcohol form by reduction or alkylation, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, ureation of amino group, sulfonylation of amino group, alkylation of amino group, substitution or amination of active halogen by amine, alkylation of hydroxy group, substitution or amination of hydroxy group can be mentioned.

[0206] In the introduction of substituent and conversion of functional group, when a reactive site possibly causing a reaction other than the desired reaction is present, a protecting group is introduced as necessary into the reactive site in advance by means known per se, the object reaction is performed, and then the protecting group is also removed by means known per se, whereby a compound within the scope of the present invention can also be produced.

[0207] When the starting compound and intermediate have an amino group, a carboxy group or a hydroxy group as a substituent, these groups may be protected by a protecting group generally used in the peptide chemistry and the like. In this case, the object compound can be obtained by eliminating the protecting group as necessary after the reaction.

[0208] Compound (I) obtained by the above-mentioned production method can be isolated and purified by a known means, such as solvent extraction, pH change of solution, phase transfer, crystallization, recrystallization, chromatography and the like.

[0209] When compound (I) has an optical isomer, a stereoisomer, a regioisomer or a rotamer, these are also encompassed in compound (I), and can be obtained as a single product according to synthesis and separation methods known per se. For example, when compound (I) contains an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I).

[0210] The optical isomer can be produced according to a method known per se.

Compound (I) may be a crystal.

[0211] A crystal of compound (I) (hereinafter sometimes to be abbreviated as the crystal of the present invention) can be produced by crystallization, by applying a crystallization method known per se.

[0212] The crystal of the present invention is superior in the physicochemical properties (e.g., melting point, solubility, stability) and biological properties (e.g., pharmacokinetics (absorbability, distribution, metabolism, excretion), efficacy), and is expected to be useful as a medicament.

compound (I) may be a pharmaceutically acceptable cocrystal or cocrystal salt. Here, the cocrystal or cocrystal salt means a crystalline substance consisting of two or more particular substances which are solids at room temperature, each having different physical properties (e.g., structure, melting point, heat of melting, hygroscopicity, solubility, stability etc.). The cocrystal and cocrystal salt can be produced by cocrystallization methods known *per se*.

[0213] Compound (I) may be a hydrate, non-hydrate, non-solvate or solvate.

[0214] Furthermore, compound (I) also encompasses a deuterium conversion form wherein ^1H is converted to $^2\text{H(D)}$.

[0215] Compound (I) may be labeled with an isotope (e.g., ^3H , ^{13}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I) and the like. Compound (I) labeled or substituted with an isotope may be used as, for example, a tracer (PET tracer) used for Positron Emission Tomography (PET), and may be useful in the fields of medical diagnosis and the like.

Compound (I) may be used as a prodrug.

[0216] The prodrug of compound (I) means a compound which is converted to compound (I) with a reaction due to an enzyme, gastric acid and the like under the physiological condition in the living body, that is, a compound which is converted to compound (I) by enzymatic oxidation, reduction, hydrolysis and the like; a compound which is converted to compound (I) by hydrolysis and the like due to gastric acid, and the like.

[0217] Examples of the prodrug for compound (I) include a compound obtained by subjecting an amino group in compound (I) to acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofurylation, pyrrolidylmethylation, pivaloyloxymethylation, tert-butylation); a compound obtained by subjecting a hydroxy group in compound (I) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonyl ethyl esterification or methylamidation) and the like. These compounds may be produced from compound (I) according to a method known *per se*.

[0218] The prodrug of compound (I) may also be one which is converted to compound (I) under physiological conditions as described in "IYAKUHIN no KAIHATSU (Development of Pharmaceuticals)", Vol. 7, Design of Molecules, p. 163-198, Published by HIROKAWA SHOTEN (1990).

[0219] In the present specification, the prodrug may form a salt. Examples of such salt include those exemplified as the salt of the aforementioned compound represented by the formula (I).

[0220] Compound (I) or a prodrug thereof (hereinafter sometimes to be simply abbreviated as the compound of the present invention) may have a superior CDK12 inhibitory activity in living organisms, and may be useful as a prophylactic or therapeutic drug for cancer, a cancer proliferation inhibitor, or a cancer metastasis inhibitor.

[0221] The compound of the present invention exhibits CDK12 inhibitory activity, and the compound of the present invention may be expected to be also superior in efficacy expression, pharmacokinetics (e.g., absorbability, distribution, metabolism, excretion), solubility (e.g., water solubility), and interaction with other pharmaceutical products (e.g., drug-metabolizing enzyme inhibitory action), stability (e.g., chemical stability, stability against enzyme), and thus the compound may be useful as a medicine.

[0222] The compound of the present invention may be expected to have low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, heart toxicity, carcinogenicity, central nervous system toxicity), and may be used administered to mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human).

[0223] The compound of the present invention may be useful as a prophylactic or therapeutic agent for pathology or disease caused by CDK12. In addition, the compound of the present invention may be superior in the selectivity for inhibiting CDK12 in the CDK subfamily and is expected to have low toxicity.

[0224] The compound of the present invention is expected to be useful for the prophylaxis or treatment of, for example, cancer [e.g., colorectal cancer (e.g., colon cancer, rectal cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophageal cancer, stomach cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma), duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer), ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testicular cancer, prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, castration-resistant prostate cancer), liver cancer (e.g., hepatoma, primary liver cancer, extrahepatic bile duct cancer), thyroid cancer (e.g., medullary thyroid carcinoma), kidney cancer (e.g., renal cell carcinoma (e.g., clear cell type renal

cell carcinoma), transitional cell carcinoma in renal pelvis and ureter), uterine cancer (e.g., cervix cancer, uterine body cancer, uterine sarcoma), gestational choriocarcinoma, brain tumor (e.g., medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, pituitary adenoma), neuroblastoma, retina blastoma, skin cancer (e.g., basalioma, malignant melanoma (melanoma)), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, spindle cell sarcoma, osteosarcoma), malignant bone tumor, bladder cancer, hematologic cancer (e.g., multiple myeloma, leukemia (e.g., acute myeloid leukemia, acute lymphocytic leukemia), malignant lymphoma, Hodgkin's disease, chronic myeloproliferative disease), cancer of unknown primary], inhibiting proliferation of cancer, suppression of metastasis, promotion of apoptosis, or prophylaxis or treatment of precancerous lesion (e.g., myelodysplastic syndrome). In addition, the compound of the present invention is expected to be useful for the prophylaxis or treatment of scleroderma, cirrhosis, idiopathic pulmonary fibrosis, inflammatory bowel disease or muscular dystrophy.

[0225] The compound of the present invention may be administered orally or parenterally to a mammal (preferably, human) as it is or as a medicament mixed with a pharmacologically acceptable carrier.

[0226] A medicament containing the compound of the present invention (sometimes to be abbreviated as "the medicament of the present invention") is described in detail below. Examples of the dosage form of the medicament of the present invention include oral preparations such as tablet (e.g., sugar-coated tablet, film-coated tablet, sublingual tablet, buccal, orally quick-integrating tablet), pill, granule, powder, capsule (e.g., soft capsule, microcapsule), syrup, emulsion, suspension, film (e.g., orally disintegrable film, mouth cavity mucosa patch film) and the like. Also, examples of the dosage form of the medicament of the present invention include parenteral agents such as injection, drip transfusion, transdermal agent (e.g., iontophoresis transdermal preparation), suppository, ointment, nasal preparation, pulmonary preparation, eye drop and the like. The medicament of the present invention may be a controlled-release preparation such as immediate-release preparation, sustained-release preparation (e.g., sustained-release microcapsule) and the like.

[0227] The medicament of the present invention may be produced by a known production method (e.g., the method described in the Japanese Pharmacopoeia) generally used in the technical field of preparation formulations. The medicament of the present invention can contain, where necessary, an appropriate amount of an additive generally used in the pharmaceutical field such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier, colorant, preservative, aromatic, corrigent, stabilizer, thickening agent and the like.

[0228] These additives can be recited as the aforementioned pharmacologically acceptable carrier.

[0229] For example, tablet may be produced using excipient, binder, disintegrant, lubricant and the like, and pill and granule may be produced using excipient, binder, disintegrant. In addition, powder and capsule may be produced using excipient and the like, syrup may be produced using sweetening agent and the like, and emulsion and suspension may be produced using suspending agent, surfactant, emulsifier and the like.

[0230] Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, microcrystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, and calcium sulfate.

[0231] Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, and glycerin.

[0232] Examples of the disintegrant include starch, and calcium carbonate.

[0233] Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, and purified talc.

[0234] Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, and simple syrup.

[0235] Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, and polyoxyl 40 stearate.

[0236] Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, and bentonite.

[0237] Examples of the emulsifier include gum arabic, tragacanth, gelatin, and polysorbate 80.

[0238] For example, when the medicament of the present invention is a tablet, the tablet may be produced according to a method known per se by adding, for example, excipient (e.g., lactose, sucrose, starch), disintegrant (e.g., starch, calcium carbonate), binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose) or lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000) to the compound of the present invention, compression molding the mixture and, where necessary, applying a coating for the purpose of taste masking, enteric property or sustainability by a coating method known per se. As the coating agent used for the coating, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethyleneglycol, Tween 80, pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (manufactured by Rohm, Germany, methacrylic acid-acrylic acid copolymer) and dye (e.g., red iron oxide, titanium dioxide) may be used.

[0239] The aforementioned injection includes intravenous injection, subcutaneous injection, intradermal injection, muscular injection, intraperitoneal injection, drip injection and the like.

[0240] Such injection may be prepared by a method known per se, that is, by dissolving, suspending or emulsifying the compound of the present invention in an aseptic aqueous solution or oily solution. Examples of the aqueous solution

include saline, isotonic solution (e.g., D-sorbitol, D-mannitol, sodium chloride) containing glucose and other auxiliary agents and the like. The aqueous solution may contain suitable solubilizing agents, for example, alcohol (e.g., ethanol), polyalcohol (e.g., propylene glycol, polyethylene glycol), non-ionic surfactant (e.g., polysorbate 80, HCO-50). Examples of the oily solution include sesame oil, soybean oil and the like. The oily solution may contain a suitable solubilizing agent. Examples of the solubilizing agent include benzyl benzoate, benzyl alcohol and the like. The injection may contain buffering agent (e.g., phosphate buffer, sodium acetate buffer), soothing agent (e.g., benzalkonium chloride, procaine hydrochloride), stabilizer (e.g., human serum albumin, polyethylene glycol), preservative (e.g., benzyl alcohol, phenol) and the like. An injection thus prepared may be generally filled in an ampoule.

[0241] While the content of the compound of the present invention in the medicament of the present invention varies depending on the preparation form, it is generally about 0.01 - about 100 wt%, preferably about 2 - about 85 wt%, further preferably about 5 - about 70 wt%, relative to the whole preparation.

[0242] While the content of the additive in the medicament of the present invention varies depending on the preparation form, it is generally about 1 to about 99.9 wt%, preferably about 10 to about 90 wt%, relative to the whole preparation.

[0243] The compound of the present invention is stable and low toxic, and may be used safely. While the daily dose of the compound of the present invention varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 1 to about 1000 mg, preferably about 3 to about 300 mg, more preferably about 10 to 200 mg, as the compound of the present invention, which may be given in a single administration or administered in 2 or 3 portions a day.

[0244] When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose of the compound of the present invention varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg - about 100 mg, preferably about 0.01 - about 50 mg, more preferably about 0.01 - about 20 mg, of the compound of the present invention relative to 1 kg of body weight, which is preferably given by intravenous injection.

[0245] The compound of the present invention may be used concurrently with other drugs. To be specific, the compound of the present invention may be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, medicaments inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

[0246] As the "hormonal therapeutic agent", for example, fosfestrol, diethylstilbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogen (e.g., tamoxifen citrate, toremifene citrate), pill preparation, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonist (e.g., goserelin acetate, buserelin, leuporelin acetate), droloxifene, epitioastanol, ethinylestradiol sulfonate, aromatase inhibitor (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane), anti-androgen (e.g., flutamide, bicartamide, nilutamide, enzalutamide), 5 α -reductase inhibitor (e.g., finasteride, epristeride, dutasteride), adrenocortical hormone drug (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone), androgen synthesis inhibitor (e.g., abiraterone), retinoid and drugs that retard retinoid metabolism (e.g., liarozole), thyroid gland hormone, and DDS (Drug Delivery System) preparation thereof are used.

[0247] As the "chemotherapeutic agents", alkylating agents, antimetabolites, anticancer antibiotics, and plant-derived anticancer agents may be used.

[0248] As the "alkylating agent", for example, nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, estramustine phosphate sodium, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, and DDS preparations thereof may be used.

[0249] As the "antimetabolite", for example, mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drug (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emitefur, capecitabine), aminopterin, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, tiazofurin, ambamustine, bendamustine, and DDS preparations thereof may be used.

[0250] As the "antitumor antibiotic", for example, actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarkomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, and DDS preparations thereof (e.g., Doxorubicin encapsulated PEG ribosome) may be used.

[0251] As the "plant-derived antitumor drug", for example, etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, cabazitaxel, vinorelbine, and DDS preparations thereof may be used.

[0252] As the "immunotherapeutic agent", for example, picibanil, krestin, schizophyllan, lentinan, ubenimex, interferon, interleukin, macrophage colony stimulating factor, granulocyte colony stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, corynebacterium parvum, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody (e.g., ipilimumab, tremelimumab), anti-PD-1 antibody (e.g., nivolumab, pembrolizumab), anti-PD-L1 antibody may be used.

[0253] The "cell growth factors" in the "medicament inhibiting actions of cell growth factor and receptor thereof" may be any substance that promotes cell proliferation, which is normally peptide having not more than 20,000 molecular weight, and capable of exhibiting the activity at low concentrations by binding to a receptor, and specifically

(1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF (e.g., TGF α);
(2) insulin or substances possessing substantially the same activity as insulin (e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2),

(3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF (e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10), and

(4) other cell growth factors (e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGF β (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin); may be used.

[0254] The "cell growth factor receptor" may be any receptor capable of binding to the aforementioned cell growth factors, and specifically, EGF receptor, heregulin receptor (e.g., HER3), insulin receptor, IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin receptor (e.g., Tie2), PDGF receptor, and the like may be used.

[0255] As the "medicament inhibiting actions of cell growth factor and receptor thereof", for example, EGF inhibitor, TGF α inhibitor, heregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGF β inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Smo inhibitor, ALK inhibitor, ROR1 inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK (MEK1/2) inhibitor, MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor, PI3K inhibitor, and the like may be used. More specifically, anti-VEGF antibody (e.g., Bevacizumab, Ramucurumab), anti-HER2 antibody (e.g., Trastuzumab, Pertuzumab), anti-EGFR antibody (e.g., Cetuximab, Panitumumab, Matuzumab, Nimotuzumab), anti-HGF antibody, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, Ibrutinib, Bosutinib, Cabozantinib, Crizotinib, Alectinib, Vismodegib, Axitinib, Motesanib, Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, Tozasertib, 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yl]oxy]propyl]-N-ethylamino]ethyl phosphate (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid, N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), Volasertib, Selumetinib, Trametinib, N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901), Bosutinib, Regorafenib, Afatinib, Idelalisib, Ceritinib, Dabrafenib, and the like may be used.

[0256] Besides the above-mentioned drugs, asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitor (e.g., irinotecan, topotecan, indotecan, Indimitecan), topoisomerase II inhibitor (e.g., sobuzoxane), differentiation-inducing factor (e.g., retinoid, vitamin D), other angiogenesis inhibitor (e.g., fumagillin, shark extract, COX-2 inhibitor), α -blocker (e.g., tamsulosin hydrochloride), bisphosphonic acid (e.g., pamidronate, zoledronate), thalidomide, lenalidomide, pomalidomide, 5-azacytidine, decitabine, proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib), NEDD8 inhibitor (e.g., Pevonedistat), UAE inhibitor, PARP inhibitor (e.g., Olaparib, Niraparib, Veliparib, Rucaparib), antitumor antibodies such as anti-CD20 antibody (e.g., Rituximab, Obinutuzumab), anti-CCR4 antibody (e.g., Mogamulizumab) and the like, antibody drug complex (e.g., trastuzumab emtansine, brenximab vedotin), and the like may also be used as a concomitant drug.

[0257] By combining the compound of the present invention and a concomitant drug, superior effects such as (1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug, (2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like), (3) the period of treatment can be set longer, (4) a sustained treatment effect can be designed, (5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

[0258] In the following, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

[0259] When the combination agent of the present invention is administered, the administration period is not limited and the compound of the present invention and the concomitant drug may be administered simultaneously, or may be administered at a time interval to an administration subject. When administered at a time interval, the interval varies depending on the effective ingredient, dosage form and administration method, and, for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 minute to 3 days, preferably from 10 minutes to 1 day, more preferably from 15 minutes to 1 hour, after administration of the concomitant drug is an example. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 minute to 1 day, preferably from 10 minutes to 6 hours, more preferably from 15 minutes to 1 hour after administration of the compound of the present invention is an example. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

[0260] As the administration mode of the compound of the present invention and the concomitant drug, the following methods can be mentioned: (1) The compound of the present invention and the concomitant drug are simultaneously formulated to give a single preparation which is administered. (2) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered by the same administration route at staggered times. (4) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered simultaneously by the different administration routes. (5) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered by the different administration routes at staggered times (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order), and the like.

[0261] The dose of the concomitant drug may be appropriately determined based on the dose employed in clinical situations. The mixing ratio of the compound of the present invention and a concomitant drug may be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like. For example, when the subject of administration is a human, 0.01 to 100 parts by weight of a concomitant drug may be used per 1 part by weight of the compound of the present invention.

[0262] Furthermore, the compound of the present invention or the combination agent of the present invention may be used in combination with a non-drug therapy. Specifically, the compound of the present invention or the combination agent of the present invention may be combined with a non-drug therapy such as (1) surgery, (2) pressurized chemotherapy using angiotensin II and the like, (3) gene therapy, (4) hyperthermic therapy, (5) cryotherapy, (6) laser cautery method, (7) radiation therapy.

[0263] For example, using the compound of the present invention or the combination agent of the present invention before or after the aforementioned surgery or the like, or before or after a treatment combining two or three kinds of these, effects such as prevention of resistance expression, elongation of disease-free period (Disease-Free Survival), suppression of cancer metastasis or recurrence, life-prolongation and the like may be achieved.

[0264] In addition, a treatment by the compound of the present invention or the combination agent of the present invention and a supporting therapy [(i) administration of various antibiotics (e.g., β -lactams such as pamporin and the like, macrolides such as clarithromycin and the like) for combination of infectious diseases, (ii) administration of intravenous hyperalimentation, amino acid preparation, general vitamin preparation for improvement of malnutrition, (iii) administration of morphine for relieving pain, (iv) administration of medicaments that improve side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, hemoglobin concentration reduction, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of medicaments that suppress resistance of cancer to multiple drugs] may also be combined.

[Example]

[0265] The present invention is further explained in detail by referring to the following Examples, Experimental Examples and Formulation Examples which do not limit the present invention and may be changed without departing from the scope of the present invention.

[0266] The "room temperature" in the following Examples indicates the range of generally from about 10°C to about 35°C. The ratio for a mixed solvent is, unless otherwise specified, a volume mixing ratio and % means wt% unless otherwise specified.

[0267] Unless particularly indicated, the elution in column chromatography in the Examples was performed under observation by TLC (Thin Layer Chromatography). For TLC observation, 60F₂₅₄ manufactured by Merck was used as

a TLC plate, and the solvent used as an elution solvent for column chromatography was used as developing solvent. For detection, moreover, a UV detector was adopted. In silica gel column chromatography, the indication of NH means use of aminopropylsilane-bonded silica gel. In preparative HPLC (high performance liquid chromatography), the indication of C18 means use of octadecyl-bonded silica gel. The ratio shown for elution solvents is, unless otherwise specified, a volume mixing ratio.

[0268] For the analysis of ^1H NMR, ACD/SpecManager (trade name) software and the like were used. Very mild peaks for protons of a hydroxy group, an amino group and the like are sometimes not described.

[0269] MS was measured by LC/MS. As ionization method, ESI method, or APCI method was used. The data indicates those found. Generally, molecular ion peaks are observed; however, they may be observed as a fragment ion. In the case of a salt, generally, a molecular ion peak or a fragment ion peak of a free form is observed.

[0270] In the following Examples, the following abbreviations are used.

mp: melting point

MS: mass spectrum

M: mol concentration

N: normality

CDCl_3 : deuteriochloroform

DMSO-d_6 : deuterodimethyl sulfoxide

^1H NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatograph mass spectrometer

ESI: electrospray ionization

APCI: atmospheric pressure chemical ionization

$\text{Pd}_2(\text{dba})_3$: tris(dibenzylideneacetone)dipalladium (0)

XANTPHOS: (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine)

TFA: trifluoroacetic acid

DIPEA: N,N-diisopropylethylamine

$\text{PdCl}_2(\text{dppf})$: dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)

$\text{PdCl}_2(\text{Amphos})_2$: dichlorobis(di-tert-butyl(4-dimethylaminophenyl)phosphine)palladium(II)

$\text{Pd}(\text{PPh}_3)_4$: tetrakis triphenylphosphinepalladium (0)

DMA: N,N-dimethylacetamide

DMF: N,N-dimethylformamide

THF: tetrahydrofuran

DME: 1,2-dimethoxyethane

MeOH: methanol

DMSO: dimethyl sulfoxide

AcOH: acetic acid

NMP: N-methylpyrrolidone

TEA: triethylamine

DMAP: 4-dimethylaminopyridine

Example 199

[0271] 3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea

A) tert-butyl (trans-4-((4-bromophenyl)amino)cyclohexyl)carbamate

[0272] A mixture of tert-butyl (trans-4-aminocyclohexyl)carbamate (1.5 g), 1-bromo-4-iodobenzene (1.98 g), XANTPHOS (0.486 g), sodium 2-methylpropane-2-olate (1.01 g) and toluene (30 mL) was deaerated and substituted with argon. To the mixture was added $\text{Pd}_2(\text{dba})_3$ (0.385 g) at room temperature, and the mixture was stirred under an argon atmosphere at 80°C overnight. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, ethyl acetate/hexane and NH, ethyl acetate/hexane) to give the title compound (1.16 g).

MS: $[\text{M}+\text{H}]^+$ 369.1, 371.1.

B) tert-butyl (trans-4-((4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)carbamate

[0273] A mixture of tert-butyl (trans-4-((4-bromophenyl)amino)cyclohexyl)carbamate (1.67 g), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.411 g), cesium carbonate (2.95 g), DMF (30 mL) and water (3 mL) was deaerated, and substituted with argon. To the mixture was added PdCl₂(Amphos)₂ (0.304 g) at room temperature, and the mixture was stirred under an argon atmosphere at 100°C overnight. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.41 g). MS: [M+H]⁺ 371.2.

C) tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)carbamate

[0274] To a mixture of tert-butyl (trans-4-((4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)carbamate (500 mg), TEA (0.563 mL) and THF (12 mL) was added benzylisocyanate (0.500 mL) at room temperature, and the mixture was stirred overnight. The reaction mixture was added to water at room temperature, and the precipitate was collected by filtration. The obtained solid was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (610 mg). MS: [M+H]⁺ 504.3.

D) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea hydrochloride

[0275] To a mixture of tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)carbamate (610 mg) and THF (15 mL) was added 4 M hydrochloric acid ethyl acetate solution (30.3 mL) at room temperature, and the mixture was stirred at room temperature for 3 hr. The mixture was concentrated under reduced pressure to give the title compound (533 mg). MS: [M+H]⁺ 404.2.

E) 3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea

[0276] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea hydrochloride (207 mg), DIPEA (0.334 mL), 2-chloro-4-((3-hydroxypropyl)amino)pyrimidine-5-carbonitrile (100 mg) and DMF (5 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained solid was washed with ethyl acetate/heptane and crystallized to give the title compound (34.4 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.99-1.20 (2H, m), 1.37 (2H, d, J = 12.7 Hz), 1.55-1.72 (2H, m), 1.72-1.98 (4H, m), 3.25-3.51 (5H, m), 3.87 (3H, s), 4.15 (2H, d, J = 5.8 Hz), 4.18-4.31 (1H, m), 4.38-4.52 (1H, m), 5.70-5.91 (1H, m), 7.11-7.52 (9H, m), 7.62 (2H, dd, J = 8.3, 2.7 Hz), 7.89 (1H, s), 8.06-8.12 (1H, m), 8.17 (1H, s).

Example 319

[0277] 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

A) tert-butyl (trans-4-((5-bromopyridin-2-yl)amino)cyclohexyl)carbamate

[0278] A mixture of tert-butyl (trans-4-aminocyclohexyl)carbamate (14.53 mL), 5-bromo-2-fluoropyridine (22.8 g), DIPEA (30.5 g) and NMP (250 mL) was stirred at 180°C for 4 hr. To the reaction mixture was added water at 0°C, and the mixture was stirred at room temperature for 1 hr. The obtained solid was collected by filtration and crystallized from ethyl acetate/heptane to give the title compound (11.62 g). MS: [M+H]⁺ 370.1.

B) 4-nitrophenyl (5-bromopyridin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate

[0279] A mixture of tert-butyl (trans-4-((5-bromopyridin-2-yl)amino)cyclohexyl)carbamate (50.96 g), DIPEA (73.3 g), 4-nitrophenyl carbonochloridate (56.6 g) and THF (600 mL) was stirred at room temperature for 4 hr. To the reaction

mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give the title compound (62.26 g).

MS: $[M+H-Boc]^+$ 435.1.

C) tert-butyl (trans-4-((benzylcarbamoyl)(5-bromopyridin-2-yl)amino)cyclohexyl)carbamate

[0280] A mixture of 4-nitrophenyl (5-bromopyridin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate (66.54 g), 1-phenylmethanamine (40.4 g) and NMP (500 mL) was stirred at 70°C overnight. To the reaction mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was stirred at room temperature for 1 hr. The obtained precipitate was collected by filtration, washed with water and crystallized from ethyl acetate/hexane to give the title compound (50.19 g).

MS: $[M+H]^+$ 503.2.

D) tert-butyl (trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

[0281] A mixture of tert-butyl (trans-4-((benzylcarbamoyl) (5-bromopyridin-2-yl)amino)cyclohexyl)carbamate (50.19 g), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (27.8 g), $PdCl_2(dppf)$ dichloromethane adduct (4.15 g), 2 M cesium carbonate aqueous solution (100 mL) and DMF (500 mL) was stirred under an argon atmosphere at 100°C for 3 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and the obtained solid was crystallized from ethyl acetate/hexane to give the title compound (42.37 g).

MS: $[M+H]^+$ 505.3.

E) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea hydrochloride

[0282] To a mixture of tert-butyl (trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (42.37 g) and THF (700 mL) was added 4 M hydrochloric acid ethyl acetate solution (70 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 9 hr. The precipitate was collected by filtration to give the title compound (40.23 g).

MS: $[M+H]^+$ 405.2.

F) 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0283] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea hydrochloride (10.01 g), 2,4-dichloropyrimidine-5-carbonitrile (4.34 g), DIPEA (8.8 g) and DMA (250 mL) was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (3.59 g).

MS: $[M+H]^+$ 542.2.

G) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0284] To a mixture of 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (150 mg) and NMP (3 mL) were added oxetan-3-amine (40.5 mg) and DIPEA (0.147 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at 60°C for 3 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) and crystallized from ethyl acetate/heptane to give the title compound (113 mg).

1H NMR (300 MHz, $DMSO-d_6$) δ 1.21-1.57 (4H, m), 1.67-1.94 (4H, m), 3.34-3.64 (1H, m), 3.89 (3H, s), 4.09-4.27 (3H,

m), 4.53-4.72 (4H, m), 4.74-5.03 (1H, m), 6.45-6.54 (1H, m), 7.15-7.33 (6H, m), 7.36-7.64 (1H, m), 7.93-8.08 (3H, m), 8.13-8.21 (1H, m), 8.23-8.31 (1H, m), 8.73-8.81 (1H, m).

Example 440

3-benzyl-1-(trans-4-((5-cyano-4-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0285] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (100 mg), (5-(methylsulfonyl)pyridin-3-yl)boronic acid (55.6 mg), PdCl₂(Amphos)₂ (12.41 mg), 2 M cesium carbonate aqueous solution (0.184 mL) and NMP (3 mL) was stirred under microwave irradiation at 100°C for 1 hr. The reaction mixture was diluted with ethyl acetate (30 mL) and water (20 mL), and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate). The residue was purified by HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium acetate-based)). To the obtained fraction was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, crystallized from DMSO and water to give the title compound (30.3 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.36-1.57 (4H, m), 1.75-2.06 (4H, m), 3.34-3.41 (3H, m), 3.59-3.77 (1H, m), 3.84-3.94 (3H, m), 4.09-4.32 (3H, m), 6.44-6.59 (1H, m), 7.14-7.35 (6H, m), 7.94-8.03 (2H, m), 8.22-8.29 (1H, m), 8.49-8.67 (1H, m), 8.70-8.78 (2H, m), 8.78-8.87 (1H, m), 9.22-9.27 (1H, m), 9.29-9.37 (1H, m).

Example 469

3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

A) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0286] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (168.7 mg), 3-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg), PdCl₂(Amphos)₂ (22.04 mg), 2 M sodium carbonate aqueous solution (0.311 mL), DME (1.2 mL) and DMF (0.6 mL) was stirred under microwave irradiation at 100°C for 1 hr. Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (210 mg).

MS: [M+H]⁺ 672.5.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0287] A mixture of 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (210 mg), 2 M hydrochloric acid methanol solution (0.469 mL) and methanol (3 mL) was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (43.2 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.32-1.59 (4H, m), 1.75-2.03 (4H, m), 2.29 (3H, d, J = 4.1 Hz), 3.55-3.73 (1H, m), 3.89 (3H, s), 4.20 (3H, d, J = 5.7 Hz), 6.49-6.60 (2H, m), 7.15-7.34 (6H, m), 7.94-8.16 (3H, m), 8.24-8.31 (1H, m), 8.59 (1H, d, J = 13.0 Hz), 8.73-8.82 (1H, m), 13.11-13.22 (1H, m).

Example 482

3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0288] A mixture of 3-methylazetidin-3-ol hydrochloride (22.91 mg), DIPEA (0.097 mL), 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (75 mg) and DMF (5 mL) was

stirred at room temperature. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/hexane/methanol) to give the title compound (48 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.39 (7H, s), 1.79 (3H, brs), 1.92 (1H, brs), 3.36-3.73 (1H, m), 3.89 (3H, s), 4.19 (7H, d, J = 5.95 Hz), 5.66 (1H, d, J = 13.79 Hz), 6.45-6.55 (1H, m), 7.16-7.31 (6H, m), 7.51 (1H, dd, J = 18.32, 7.84 Hz), 7.95-8.02 (2H, m), 8.16 (1H, d, J = 16.63 Hz), 8.26 (1H, d, J = 3.31 Hz), 8.76 (1H, dd, J = 3.76 Hz).

Example 483

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea

A) tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)amino)cyclohexyl)carbamate

[0289] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(4-bromophenyl)amino)cyclohexyl)carbamate (2.5 g), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (1.755 g), PdCl₂(dppf) methylene chloride adduct (0.406 g), cesium carbonate (3.24 g), water (5 mL) and DMF (50 mL) was stirred under an argon atmosphere at 90°C for 2 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.09 g).

MS: [M+H]⁺ 531.3.

B) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea hydrochloride

[0290] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)amino)cyclohexyl)carbamate (2.09 g), 4 M hydrochloric acid ethyl acetate solution (50 mL) and MeOH (90 mL) was stirred at room temperature for 18 hr. The solvent was evaporated under reduced pressure, and the precipitate was suspended in ethyl acetate and diisopropyl ether and collected by filtration to give the title compound (1.67 g).

MS: [M+H]⁺ 431.2.

C) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea

[0291] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea hydrochloride (107.1 mg), 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (58.4 mg), DIPEA (148 mg) and NMP (2 mL) was stirred at room temperature for 16 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) and crystallized from ethanol and hexane to give the title compound (17.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.99-1.21 (2H, m), 1.26-1.49 (2H, m), 1.73-1.96 (4H, m), 3.37-3.48 (1H, m), 3.52 (3H, s), 4.16 (2H, d, J = 5.7 Hz), 4.19-4.37 (1H, m), 4.49-4.70 (4H, m), 4.71-5.05 (1H, m), 5.72-5.94 (1H, m), 6.41-6.58 (1H, m), 7.12-7.43 (7H, m), 7.53-7.92 (4H, m), 7.93-8.09 (1H, m), 8.10-8.31 (2H, m).

Example 485

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-yloxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

A) 2-chloro-4-(oxetan-3-yloxy)pyrimidine-5-carbonitrile

[0292] To a mixture of sodium hydride (60% oil dispersion, 25.3 mg) and THF (8 mL) was added oxetan-3-ol (46.8 mg) and the mixture was stirred at 0°C for 10 min. To the mixture was added 2,4-dichloropyrimidine-5-carbonitrile (100 mg) at 0°C and the mixture was stirred for 1 hr. To the reaction mixture were added saturated ammonium chloride aqueous solution and ethyl acetate, and the mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (58 mg).

MS: [M+H]⁺ 212.0.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-yloxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0293] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea hydrochloride (101 mg), 2-chloro-4-(oxetan-3-yloxy)pyrimidine-5-carbonitrile (58 mg), DIPEA (0.14 mL) and DMF (5 mL) was stirred at room temperature for 2 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (59 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.56 (4H, m), 1.73-1.91 (4H, m), 3.60 (1H, dt, J = 12.18, 6.09 Hz), 3.34-3.49 (1H, m), 3.89 (3H, s), 4.13-4.23 (3H, m), 4.56-4.64 (2H, m), 4.72-4.78 (1H, m), 4.80-4.91 (1H, m), 5.53-5.62 (1H, m), 6.45-6.52 (1H, m), 7.16-7.32 (6H, m), 7.97-8.07 (2H, m), 8.21-8.32 (1H, m), 8.47-8.51 (1H, m), 8.76 (1H, dd, J = 4.18 Hz).

Example 495

3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

A) tert-butyl (trans-4-((5-bromopyrazin-2-yl)amino)cyclohexyl)carbamate

[0294] To a mixture of tert-butyl (trans-4-aminocyclohexyl)carbamate (20 g) and 1-butanol (100 mL) were added 2,5-dibromopyrazine (26.6 g) and DIPEA (24.1 g), and the mixture was stirred under reflux overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (22.8 g).

MS: [M+H-tBu]⁺ 315.1.

B) tert-butyl (trans-4-((5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0295] A mixture of tert-butyl (trans-4-((5-bromopyrazin-2-yl)amino)cyclohexyl)carbamate (1.1 g), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (936 mg), PdCl₂(dppf) (220 mg), cesium carbonate (2 g), water and dioxane (1:10) (10 mL) was stirred under a nitrogen atmosphere at 110°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (810 mg). MS: [M+H]⁺ 373.3.

C) 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)-cyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0296] To a solution of tert-butyl (trans-4-((5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (9 g) in THF (80 mL) were added 4-nitrophenyl carbonochloridate (7.3 g) and DIPEA (6.2 g), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (10.2 g).

MS: [M+H-tBu]⁺ 482.2.

D) tert-butyl (trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0297] A mixture of 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate (10 g), 1-phenylmethanamine (12 g) and DMF (20 mL) was stirred at 70°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (3.7 g).

MS: [M+H]⁺ 506.3.

E) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea trifluoroacetate

[0298] A mixture of tert-butyl (trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (3.70 g), TFA (5 mL) and dichloromethane (10 mL) was stirred at room temperature for 2 hr. The reaction mixture was evaporated under reduced pressure to give the title compound (3.7 g).

MS: [M+H]⁺ 406.4.

F) 3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0299] A mixture of 2-chloro-4-(5-cyano-2-thienyl)pyrimidine-5-carbonitrile (45.6 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea trifluoroacetate (80 mg), DIPEA (0.134 mL) and DMF (3 mL) was stirred at room temperature for 2 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/hexane/methanol) to give the title compound (25 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.36-1.55 (4H, m), 1.80-1.93 (3H, m), 1.93-2.04 (1H, m), 3.52-3.78 (1H, m), 3.92 (3H, s), 4.16-4.30 (3H, m), 6.79-6.87 (1H, m), 7.18-7.33 (5H, m), 8.07-8.18 (3H, m), 8.39-8.53 (3H, m), 8.78 (1H, d, J = 10.20 Hz), 8.91 (1H, dd, J = 11.38, 1.37 Hz).

Example 527

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea

A) 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile

[0300] To a mixture of 2,4-dichloropyrimidine-5-carbonitrile (2.36 g) and THF (50 mL) was added oxetan-3-amine (0.991 g) at 0°C. The reaction mixture was stirred under a nitrogen atmosphere at 0°C for 1 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (753.2 mg). MS: [M+H]⁺ 211.0.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea

[0301] To a mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (54.8 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea hydrochloride (104.3 mg) and NMP (2 mL) was added DIPEA (153 mg) at room temperature. The reaction mixture was stirred at room temperature for 16 hr. To the reaction mixture was added at room temperature water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and crystallized from ethanol and hexane to give the title compound (37 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.06-1.20 (2H, m), 1.28-1.49 (2H, m), 1.69-1.97 (4H, m), 3.44 (1H, qd, J = 7.0, 5.1 Hz), 3.87 (3H, s), 4.15 (2H, d, J = 5.8 Hz), 4.24 (1H, t, J = 11.6 Hz), 4.32-4.70 (4H, m), 4.72-5.04 (1H, m), 5.70-5.89 (1H, m), 7.09-7.21 (5H, m), 7.23-7.32 (2H, m), 7.33-7.69 (3H, m), 7.84-7.92 (1H, m), 7.93-8.06 (1H, m), 8.11-8.22 (2H, m).

Example 530

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea

A) tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)amino)cyclohexyl)carbamate

[0302] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(4-bromophenyl)amino)cyclohexyl)carbamate (6.2 g), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (2.8 g), Pd(PPh₃)₄ (0.72 g), potassium carbonate (2.6 g), dioxane (40 mL) and water (10 mL) was stirred under a nitrogen atmosphere at 100°C for 2 hr. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane/methanol) to give the title compound (4.2 g).

MS: [M+H]⁺ 531.1.

B) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea hydrochloride

[0303] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ami-

no)cyclohexyl)carbamate (4.2 g) and 4 M hydrochloric acid dioxane solution (30 mL) was stirred at room temperature for 4 hr. The solvent was evaporated under reduced pressure to give the title compound (3.1 g).

MS: $[M+H]^+$ 431.3.

- 5 C) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydro-
dropyridin-4-yl)phenyl)urea

[0304] To a mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (53.6 mg), 1-(trans-4-aminocyclohexyl)-
3-benzyl-1-(4-(1-methyl-2-oxo-1,2-dihydrodropyridin-4-yl)phenyl)urea hydrochloride (111.2 mg) and NMP (2 mL) was added
10 DIPEA (0.207 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr. To the reaction
mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was
separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was
evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/meth-
15 anol) and crystallized from ethyl acetate and hexane. The obtained crude crystal was purified by silica gel column
chromatography (NH, ethyl acetate/methanol) and crystallized from ethanol and hexane to give the title compound (29.1
mg).

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.06-1.23 (2H, m), 1.26-1.48 (2H, m), 1.73-1.96 (4H, m), 3.28-3.40 (1H, m), 3.46 (3H,
s), 4.15 (2H, d, $J = 5.9$ Hz), 4.20-4.31 (1H, m), 4.47-4.61 (3H, m), 4.68 (1H, t, $J = 6.8$ Hz), 4.73-5.03 (1H, m), 5.88-6.03
(1H, m), 6.56-6.67 (1H, m), 6.69-6.80 (1H, m), 7.10-7.66 (8H, m), 7.74-7.89 (3H, m), 7.92-8.07 (1H, m), 8.13-8.21 (1H, m).

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Example 532

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-
yl)pyridazin-3-yl)urea

25

A) tert-butyl (trans-4-((6-bromopyridazin-3-yl)amino)cyclohexyl)carbamate

[0305] A mixture of tert-butyl (trans-4-aminocyclohexyl)carbamate (20 g), 3,6-dibromopyridazine (26.6g), DIPEA
(24.1g) and 1-butanol (100 mL) was stirred with heating under reflux overnight. To the reaction mixture was added water
30 at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with
water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced
pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title
compound (26.4 g).

MS: $[M+H]^+$ 371.1.

35

B) 4-nitrophenyl (6-bromopyridazin-3-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate

[0306] To a mixture of tert-butyl (trans-4-((6-bromopyridazin-3-yl)amino)cyclohexyl)carbamate (20 g) and THF (100
mL) were added 4-nitrophenyl carbonochloridate (13 g) and DIPEA (13.9 g) at room temperature. The reaction mixture
40 was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give the title compound
(28.9 g).

MS: $[M+H-tBu]^+$ 480.1.

45

C) tert-butyl (trans-4-((benzylcarbamoyl)(6-bromopyridazin-3-yl)amino)cyclohexyl)carbamate

[0307] A mixture of 4-nitrophenyl (6-bromopyridazin-3-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate
(28.9 g), 1-phenylmethanamine (6.9 g) and THF (100 mL) was stirred at 50°C overnight. To the reaction mixture was
added water, and the mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous
magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column
50 chromatography (ethyl acetate/petroleum ether) to give the title compound (7.2 g). MS: $[M+H]^+$ 504.3.

D) tert-butyl (trans-4-((benzylcarbamoyl)(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)amino)cyclohexyl)carbamate

[0308] A mixture of tert-butyl (trans-4-((benzylcarbamoyl) (6-bromopyridazin-3-yl)amino)cyclohexyl)carbamate (343
mg), $\text{PdCl}_2(\text{dppf})$ (50 mg), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (211 mg), cesium car-
bonate (443 mg), dioxane and water (10:1) (10 mL) was stirred under a nitrogen atmosphere at 110°C overnight. The
solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography
(ethyl acetate/petroleum ether) to give the title compound (220 mg).

55

MS: $[M+H]^+$ 506.4.

E) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea hydrochloride

- 5 **[0309]** A mixture of tert-butyl (trans-4-((benzylcarbamoyl) (6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)amino)cyclohexyl)carbamate (2.8 g) and 4 M hydrochloric acid dioxane solution (10 mL) was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (2.3 g).

MS: $[M+H-tBu]^+$ 406.3.

- 10 F) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

- 15 **[0310]** To a mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (49.6 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea hydrochloride (99 mg) and NMP (2 mL) was added DIPEA (0.195 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) and crystallized from ethanol and hexane to give the title compound (40.6 mg).

- 20 1H NMR (300 MHz, DMSO- d_6) δ 1.25-1.59 (4H, m), 1.85 (4H, d, J = 12.9 Hz), 3.37-3.69 (1H, m), 3.93 (3H, s), 4.14-4.36 (3H, m), 4.49-4.72 (4H, m), 4.76-5.07 (1H, m), 6.87 (1H, t, J = 5.8 Hz), 7.11-7.36 (5H, m), 7.38-7.69 (2H, m), 7.88-8.11 (2H, m), 8.11-8.24 (2H, m), 8.40-8.57 (1H, m).

Example 536

- 25 3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

- 30 A) 2-(methylsulfanyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidine-5-carbonitrile

- 35 **[0311]** A mixture of 4-chloro-2-(methylsulfanyl)pyrimidine-5-carbonitrile (0.98 g), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.615 g), $PdCl_2(Amphos)_2$ (0.374 g), 2 M sodium carbonate aqueous solution (5.28 mL) and DME (13 mL) was stirred under microwave irradiation at 100°C for 1 hr. Insoluble material was filtered off, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (0.9 g). 1H NMR (300 MHz, DMSO- d_6) δ 1.43-1.57 (3H, m), 1.92-2.05 (2H, m), 2.22-2.39 (1H, m), 2.64 (3H, s), 3.43-3.55 (1H, m), 3.74-3.85 (1H, m), 6.02 (1H, dd, J = 9.3, 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.76 (1H, d, J = 2.0 Hz), 9.18 (1H, s).

- 40 B) 2-(methylsulfanyl)-4-(1H-pyrazol-5-yl)pyrimidine-5-carbonitrile

- 45 **[0312]** A mixture of 2-(methylsulfanyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidine-5-carbonitrile (0.8 g), 6 M aqueous hydrochloric acid solution (1.327 mL) and MeOH (10 mL) was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (0.33 g). MS: $[M+H]^+$ 218.1.

C) 2-chloro-4-(4-chloro-1H-pyrazol-5-yl)pyrimidine-5-carbonitrile

- 50 **[0313]** To a mixture of 2-(methylsulfanyl)-4-(1H-pyrazol-5-yl)pyrimidine-5-carbonitrile (49 mg) and acetonitrile (5 mL) was added sulfuryl dichloride (152 mg) at 0°C. The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate and diisopropyl ether to give the title compound (22.6 mg).

- 55 MS: $[M+H]^+$ 240.0.

D) 3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0314] A mixture of 2-chloro-4-(4-chloro-1H-pyrazol-5-yl)pyrimidine-5-carbonitrile (22.6 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (41.4 mg), potassium carbonate (26 mg) and DMF (1 mL) was stirred at 60°C for 3 hr was stirred. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (13 mg).

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.35-1.53 (4H, m), 1.75-2.03 (4H, m), 3.58-3.77 (1H, m), 3.89 (3H, s), 4.15-4.30 (3H, m), 6.47-6.57 (1H, m), 7.15-7.36 (6H, m), 7.96-8.03 (2H, m), 8.14-8.19 (1H, m), 8.23-8.31 (2H, m), 8.62-8.79 (2H, m), 13.72-13.84 (1H, m).

Example 538

3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

[0315] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea hydrochloride (40.7 mg), 2-chloro-4-(5-cyano-2-thienyl)pyrimidine-5-carbonitrile (25 mg), DIPEA (0.08 mL) and DMF (3 mL) was stirred at room temperature for 2 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/hexane/methanol) to give the title compound (23.8 mg). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.39-1.60 (4H, m), 1.81-2.22 (4H, m), 3.55-3.75 (1H, m), 3.93 (3H, s), 4.19-4.34 (3H, m), 6.90 (1H, d, J = 4.89 Hz), 7.18-7.33 (5H, m), 7.53 (1H, t, J = 8.56 Hz), 7.97 (1H, t, J = 8.64 Hz), 8.09 (1H, t, J = 4.20 Hz), 8.16 (2H, t, J = 4.67 Hz), 8.45-8.54 (2H, m), 8.78 (1H, d, J = 8.31 Hz).

Example 539

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0316] To a mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (30.5 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea trifluoroacetate (72.1 mg) and NMP (1.5 mL) was added DIPEA (0.121 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (21.9 mg). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.26-1.46 (4H, m), 1.73-1.93 (4H, m), 3.36-3.64 (1H, m), 3.92 (3H, s), 4.20 (3H, d, J = 5.9 Hz), 4.52-5.06 (5H, m), 6.73-6.87 (1H, m), 7.11-7.65 (6H, m), 7.91-8.22 (3H, m), 8.35-8.46 (2H, m), 8.82-8.95 (1H, m).

Example 542

3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

A) 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

[0317] A mixture of 2,4-dichloropyrimidine-5-carbonitrile (0.368 g), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea hydrochloride (0.85 g), DIPEA (1.243 g) and DMA (15 mL) was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (223.8 mg).

MS: [M+H]⁺ 543.2.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

[0318] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

zol-4-yl)pyridazin-3-yl)urea (78 mg), 3-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (46.2 mg), PdCl₂(Amphos)₂ (10.17 mg), 2 M sodium carbonate aqueous solution (0.144 mL), DME (1 mL) and DMF (0.5 mL) was stirred under microwave irradiation at 100°C for 1 hr. Insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (86 mg).

MS: [M+H]⁺ 673.3.

C) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea

[0319] A mixture of 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea (86 mg) and TFA (1 mL) was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (27.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.35-1.62 (4H, m), 1.78-2.04 (4H, m), 2.23-2.32 (3H, m), 3.60-3.75 (1H, m), 3.93 (3H, s), 4.17-4.35 (3H, m), 6.54-6.61 (1H, m), 6.84-6.94 (1H, m), 7.16-7.36 (5H, m), 7.52 (1H, dd, J = 9.0, 4.7 Hz), 7.92-8.02 (1H, m), 8.05-8.22 (2H, m), 8.47 (1H, d, J = 1.4 Hz), 8.59 (1H, d, J = 10.8 Hz), 13.11-13.23 (1H, m).

Example 552

3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

A) 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0320] A mixture of 2,4-dichloropyrimidine-5-carbonitrile (236 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea trifluoroacetate (641.2 mg), DIPEA (1.078 mL) and DMA (10 mL) was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (192.9 mg).

MS: [M+H]⁺ 543.2.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0321] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea (64.9 mg), 3-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (38.4 mg), PdCl₂(Amphos)₂ (8.46 mg), 2 M sodium carbonate aqueous solution (0.12 mL), THF (0.5 mL) and DMF (0.25 mL) was stirred under microwave irradiation at 100°C for 1 hr. Insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (61.1 mg).

MS: [M-H]⁻ 671.3.

C) 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0322] A mixture of 3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea (61.1 mg) and TFA (1 mL) was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (9.4 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.34-1.55 (4H, m), 1.80-2.01 (4H, m), 2.24-2.32 (3H, m), 3.58-3.76 (1H, m), 3.92 (3H, s), 4.16-4.32 (3H, m), 6.58 (1H, d, J = 4.3 Hz), 6.76-6.87 (1H, m), 7.15-7.35 (5H, m), 8.04-8.16 (2H, m), 8.39-8.45 (2H,

m), 8.59 (1H, d, J = 13.0 Hz), 8.87-8.94 (1H, m), 13.11-13.21 (1H, m).

Example 553

5 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

A) tert-butyl (trans-4-((benzylcarbamoyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

10 **[0323]** A mixture of (2-methoxypyrimidin-5-yl)boronic acid (1.376 g), tert-butyl (trans-4-((benzylcarbamoyl)(5-bromopyridin-2-yl)amino)cyclohexyl)carbamate (3 g), PdCl₂ (Amphos)₂ (0.401 g), 2 M cesium carbonate aqueous solution (5.96 mL) and DMF (60 mL) was stirred at 80°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (2.62 g).
15 MS: [M+H]⁺ 533.3.

B) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

20 **[0324]** A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (2.12 g) and TFA (50 mL) was stirred at room temperature for 1 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (1.722 g).
25 MS: [M+H]⁺ 433.3.

C) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

30 **[0325]** A mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (35 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (41.4 mg), DIPEA (0.067 mL) and NMP (3 mL) was stirred at room temperature overnight. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium bicarbonate-based)). The obtained fraction was concentrated under reduced pressure, and the obtained solid was treated with ethyl acetate and diisopropyl ether to give the title compound (18.2 mg).
35 ¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.46 (2H, m), 1.46-1.66 (2H, m), 1.75-1.93 (4H, m), 3.38-3.65 (1H, m), 3.98 (3H, s), 4.15-4.29 (3H, m), 4.55-5.06 (5H, m), 6.75-6.88 (1H, m), 7.18-7.41 (6H, m), 7.63 (1H, d, J = 7.13 Hz), 7.95-8.09 (1H, m), 8.15-8.24 (2H, m), 8.88-8.92 (1H, m), 9.04 (2H, s).

40 Example 566

3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-6-azaspiro[3.4]octa-6-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

45 A) 3-benzyl-1-(trans-4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0326] To a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (1.48 g), dichloroethane and tert-butanol (1:1) (15 mL) was added 1 M zinc chloride tetrahydrofuran solution (13.6 mL) under a nitrogen atmosphere 0°C. The mixture was stirred for 1 hr, and 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea hydrochloride (600 mg) and TEA (275 mg) were added at the same temperature. The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted with dichloromethane. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (0.1% trifluoroacetic acid-based)) to give the title compound (140 mg).
55 MS: [M+H]⁺ 585.2.

B) 3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-6-azaspiro[3.4]octa-6-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0327] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (60 mg), 2-oxa-6-azaspiro[3.4]octane (12.8 mg), DIPEA (40.1 mg) and DMF (2 mL) was stirred at 60°C for 3 hr. The reaction mixture was purified by HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (0.1% trifluoroacetic acid-based)) to give the title compound (25.2 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.31-1.43 (4H, m), 1.79-1.81 (3H, m), 1.94-1.97 (1H, m), 2.13-2.15 (2H, m), 3.49 (3H, t, J = 6.4 Hz), 3.70 (2H, s), 3.89 (3H, s), 4.18-4.20 (3H, m), 4.48-4.51 (4H, m), 6.49-6.51 (1H, m), 7.17-7.23 (5H, m), 7.27-7.31 (2H, m), 7.99-8.02 (2H, m), 8.10-8.15 (1H, m), 8.27 (1H, s), 8.76-8.78 (1H, m).

Example 574

3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0328] A mixture of 3-benzyl-1-(trans-4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (55.0 mg), oxetan-3-amine (7.56 mg) and DMF (2 mL) was stirred at 60°C for 4 hr. The reaction mixture was purified by HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (0.1% trifluoroacetic acid-based)) to give the title compound (21.6 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.31-1.41 (4H, m), 1.79-1.90 (4H, m), 3.31-3.53 (1H, m), 3.89 (3H, s), 4.14-4.20 (3H, m), 4.56-4.71 (4H, m), 4.76-4.97 (1H, m), 6.49-6.54 (1H, m), 7.06-7.37 (8H, m), 7.98-8.06 (3H, m), 8.26-8.28 (1H, m), 8.76-8.78 (1H, m).

Example 575

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea

A) tert-butyl (trans-4-((5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate

[0329] A mixture of tert-butyl (trans-4-aminocyclohexyl)carbamate (28.3 g), 5-bromo-2-chloropyrimidine (25 g), DIPEA (56 mL) and 1-butanol (150 mL) was stirred at 110°C for 16 hr. The solvent was evaporated under reduced pressure. To the residue were added ethanol (100 mL) and water (100 mL) at room temperature, and the mixture was stirred for 30 min. The obtained solid was collected by filtration, and washed with water and 2-propanol to give the title compound (41.5 g).

MS: [M+H-tBu]⁺ 315.0.

B) 4-nitrophenyl (5-bromopyrimidin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate

[0330] To a mixture of tert-butyl (trans-4-((5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate (9.17 g), DIPEA (17.25 mL) and THF (120 mL) was added 4-nitrophenyl carbonochloridate (15.96 g) at room temperature. The reaction mixture was stirred at room temperature for 16 hr. Insoluble material was filtered off, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (13.02 g). MS: [M+H-tBu]⁺ 480.0.

C) tert-butyl (trans-4-((benzylcarbamoyl)(5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate

[0331] To a mixture of 4-nitrophenyl (5-bromopyrimidin-2-yl)(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate (13.02 g) and NMP (150 mL) was added 1-phenylmethanamine (7.8 g) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at 70°C for 2 hr. To the reaction mixture was added water, and the resulting solid was collected by filtration and washed with water and diisopropyl ether to give the title compound (8.1 g).

MS: [M+H]⁺ 504.1.

D) tert-butyl (trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate

[0332] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate (1.7 g), PdCl₂(dppf) (310 mg), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.7 g), 2 M sodium car-

bonate aqueous solution (3.37 mL) and DME (50 mL) was stirred under a nitrogen atmosphere at 80°C for 6 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.435 g).

MS: [M+H]⁺ 506.3.

E) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea hydrochloride

[0333] To a mixture of tert-butyl (trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (112.5 mg) and THF (1 mL) was added 4 M hydrochloric acid ethyl acetate solution (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr, and the solvent was evaporated under reduced pressure to give the title compound (92.3 mg).

MS: [M+H]⁺ 406.1.

F) 3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea

[0334] To a mixture of 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (36.1 mg), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea hydrochloride (46.1 mg) and NMP (2 mL) was added DIPEA (0.091 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr, and 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (17.1 mg) was added. The reaction mixture was stirred at 70°C for 2 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate and ethanol to give the title compound (31.7 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.27-1.49 (2H, m), 1.62-2.01 (4H, m), 2.07-2.28 (2H, m), 3.51-3.83 (1H, m), 3.88 (3H, s), 4.32-4.74 (7H, m), 4.76-5.06 (1H, m), 7.16-7.38 (5H, m), 7.40-7.73 (1H, m), 7.95 (1H, s), 7.97-8.14 (1H, m), 8.15-8.32 (2H, m), 8.78-8.91 (2H, m), 9.03 (1H, t, J = 5.7 Hz).

Example 577

3-benzyl-1-(trans-4-((5-cyano-4-(5-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

A) 4-(3-methyl-1H-pyrazol-4-yl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile

[0335] A mixture of 4-chloro-2-(methylsulfanyl)pyrimidine-5-carbonitrile (966 mg), tert-butyl 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (3.22 g), PdCl₂(Amphos)₂ (193.8 mg), 2 M sodium carbonate aqueous solution (5.2 mL) and DME (30 mL) was stirred under a nitrogen atmosphere at 80°C for 16 hr. Insoluble material was filtered off, 1 M aqueous hydrochloric acid solution was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and treated with diisopropyl ether to give the title compound (629.9 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.57 (3H, s), 2.60 (3H, s), 8.37 (1H, brs), 8.95 (1H, s), 13.36 (1H, brs).

B) 2-chloro-4-(5-methyl-1H-pyrazol-4-yl)pyrimidine-5-carbonitrile

[0336] To a mixture of 4-(3-methyl-1H-pyrazol-4-yl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile (164.5 mg) and acetic acid (10 mL) was added sulfuryl dichloride (0.288 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure. The residue was washed with diisopropyl ether to give the title compound (103.9 mg).

MS: [M+H]⁺ 220.1.

C) 3-benzyl-1-(trans-4-((5-cyano-4-(5-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0337] A mixture of DIPEA (0.12 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (74 mg), 2-chloro-4-(5-methyl-1H-pyrazol-4-yl)pyrimidine-5-carbonitrile (37.6 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl ace-

tate/hexane/methanol) to give the title compound (12.8 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.36-1.68 (4H, m), 1.77-2.06 (4H, m), 2.16-2.80 (3H, m), 3.54-3.74 (1H, m), 3.99 (3H, s), 4.17-4.31 (3H, m), 6.70-6.93 (1H, m), 7.18-7.36 (6H, m), 7.87-8.48 (3H, m), 8.54-8.61 (1H, m), 8.90 (1H, t, J = 3.36 Hz), 9.02-9.07 (2H, m), 12.94-13.23 (1H, m).

5 Example 581

benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

10 A) benzyl (5-bromopyridin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate

[0338] To a mixture of tert-butyl (trans-4-((5-bromopyridin-2-yl)amino)cyclohexyl)carbamate (5.08 g), and THF (70 mL) were added DIPEA (7.31 mL) and benzyl carbonochloridate (3.09 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. DIPEA (7.31 mL) and benzyl carbonochloridate (3.09 mL) were further added, and the reaction mixture was stirred under a nitrogen atmosphere at room temperature for 6 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (5.2 g). MS: [M+H]⁺ 504.2.

20 B) benzyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0339] A mixture of benzyl (5-bromopyridin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate (5 g), (2-methoxypyrimidin-5-yl)boronic acid (2.289 g), PdCl₂(dppf) (0.725 g), cesium carbonate (6.46 g) and DMF (100 mL) was stirred at 110°C for 3 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (3.83 g). MS: [M+H]⁺ 534.2.

30 C) benzyl (trans-4-aminocyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0340] A mixture of benzyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (200 mg) and TFA (4 mL) was stirred at room temperature for 2 hr, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (34 mg). MS: [M+H]⁺ 434.2.

40 D) benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0341] A mixture of DIPEA (0.055 mL), benzyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (34 mg), 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (18.17 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (7.2 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.44 (2H, m), 1.48-1.73 (2H, m), 1.80-1.99 (4H, m), 3.35-3.67 (1H, m), 3.98 (3H, s), 4.08 (1H, brs), 4.55-4.98 (5H, m), 5.12 (2H, s), 7.17-7.65 (7H, m), 7.90-8.26 (3H, m), 8.84-8.92 (1H, m), 9.04 (2H, s).

50 Example 582

1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-fluorobenzyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

55 A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

[0342] A mixture of benzyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (3.48 g), 10% palladium-carbon (1.5 g) and MeOH (400 mL) was stirred under a hydrogen atmosphere at normal pressure at room temperature for 1 hr. The catalyst was filtered off, and the filtrate was concentrated under

reduced pressure to give the title compound (2.599 g).

MS: [M+H]⁺ 400.3.

B) 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0343] To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (1.05 g), DIPEA (2 mL) and THF (25 mL) was added 4-nitrophenyl carbonochloridate (1.59 g) at 0°C. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. Insoluble material was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.44 g). MS: [M+H]⁺ 565.3.

C) tert-butyl (trans-4-(((2-fluorobenzyl)carbamoyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

[0344] A mixture of 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)-cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (185 mg), 1-(2-fluorophenyl)methanamine (123 mg) and NMP (10 mL) was stirred at 70°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (180 mg). MS: [M+H]⁺ 551.1.

D) 1-(trans-4-aminocyclohexyl)-3-(2-fluorobenzyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0345] A mixture of tert-butyl (trans-4-(((2-fluorobenzyl)carbamoyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (180 mg) and TFA (4 mL) was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (60 mg). MS: [M+H]⁺ 451.3.

E) 1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-fluorobenzyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0346] A mixture of DIPEA (0.093 mL), 1-(trans-4-aminocyclohexyl)-3-(2-fluorobenzyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (60 mg), 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (30.9 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (20.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.44 (2H, m), 1.44-1.65 (2H, m), 1.75-1.93 (4H, m), 3.36-3.64 (1H, m), 3.98 (3H, s), 4.13-4.30 (3H, m), 4.54-4.72 (4H, m), 4.74-5.01 (1H, m), 6.72-6.84 (1H, m), 7.01-7.72 (6H, m), 7.84-8.09 (1H, m), 8.15-8.26 (2H, m), 8.89-8.94 (1H, m), 9.05 (2H, s).

Example 587

N-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide

A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)(phenoxyacetyl)amino)cyclohexyl)carbamate

[0347] To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (500 mg), DIPEA (0.7 mL) and THF (10 mL) was added phenoxyacetyl chloride (0.35 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (660 mg). MS: [M+H]⁺ 534.3.

B) N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide

[0348] To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)(phenoxyacetyl)amino)cyclohexyl)carbamate (655 mg) and acetonitrile (3 mL) was added TFA (1.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hr, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (520 mg). MS: [M+H]⁺ 434.2.

C) N-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide

[0349] A mixture of DIPEA (0.063 mL), N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide (39 mg), 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (20.84 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (14.7 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.29-1.55 (4H, m), 1.79-2.01 (4H, m), 3.38-3.65 (1H, m), 3.99 (3H, s), 4.24-4.46 (3H, m), 4.54-4.72 (4H, m), 4.74-5.03 (1H, m), 6.75 (2H, d, J = 7.84 Hz), 6.91 (1H, t, J = 7.25 Hz), 7.24 (2H, t, J = 7.32 Hz), 7.35-7.72 (2H, m), 7.91-8.09 (1H, m), 8.13-8.21 (1H, m), 8.30-8.39 (1H, m), 8.94-9.03 (1H, m), 9.04-9.13 (2H, m).

Example 588

3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

A) 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine

[0350] To a mixture of oxetan-3-ol (1.88 g) and THF (100 mL) was added sodium hydride (60% oil dispersion, 1.133 g) at 0°C. The mixture was stirred under a nitrogen atmosphere at 0°C for 30 min and was added to a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (5.23 g) and THF (10 mL) at 0°C. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. To the reaction mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (782.7 mg).

MS: [M+H]⁺ 255.0.

B) 3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0351] A mixture of DIPEA (0.081 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (50 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (32.4 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (7.1 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.32-1.49 (2H, m), 1.49-1.72 (2H, m), 1.76-1.95 (4H, m), 3.30 (1H, s), 3.98 (3H, s), 4.14-4.28 (3H, m), 4.50-4.64 (2H, m), 4.74-4.93 (2H, m), 5.51-5.65 (1H, m), 6.50-6.95 (1H, m), 7.11-7.44 (6H, m), 7.71-8.03 (1H, m), 8.15-8.27 (1H, m), 8.28-8.37 (1H, m), 8.88-8.95 (1H, m), 9.05 (2H, d, J = 2.08 Hz).

Example 589

3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

A) 2-chloro-N-(oxetan-3-yl)-5-(trifluoromethyl)pyrimidine-4-amine

[0352] To a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (4.8 g), DIPEA (7.7 mL) and THF (100 mL) was added oxetan-3-amine (1.552 mL) at 0°C. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 7 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The

solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.3 g).

MS: [M+H]⁺ 254.0.

- 5 B) 3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0353] A mixture of DIPEA (0.162 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (100 mg), 2-chloro-N-(oxetan-3-yl)-5-(trifluoromethyl)pyrimidine-4-amine (64.5 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (16.6 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.24-1.42 (2H, m), 1.42-1.69 (2H, m), 1.76-1.94 (4H, m), 3.37-3.68 (1H, m), 3.98 (3H, s), 4.15-4.27 (3H, m), 4.54-4.72 (4H, m), 4.75-5.00 (1H, m), 6.64-6.89 (1H, m), 7.08-7.37 (8H, m), 8.00-8.05 (1H, m), 8.22 (1H, dd, J = 8.31, 2.64 Hz), 8.90 (1H, s), 9.04 (2H, s).

Example 592

3-benzyl-1-(trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

- A) 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)azepan-4-ol

[0354] To a mixture of azepan-4-ol hydrochloride (680 mg), DIPEA (2.39 mL) and THF (30 mL) was added a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (993 mg) and THF (10 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 2 days. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (201.5 mg).

MS: [M+H]⁺ 296.2.

- B) 3-benzyl-1-(trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0355] A mixture of DIPEA (0.081 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (50 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)azepan-4-ol (37.6 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) and HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium bicarbonate-based)) to give the title compound (6 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.27-2.04 (14H, m), 3.38-3.73 (6H, m), 3.98 (3H, s), 4.15-4.28 (3H, m), 4.51 (1H, d, J = 3.97 Hz), 6.65-7.09 (1H, m), 7.18-7.34 (7H, m), 8.11-8.23 (2H, m), 8.89 (1H, d, J = 1.89 Hz), 9.04 (2H, s).

Example 595

3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0356] A mixture of DIPEA (0.07 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (50 mg), 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile (35 mg) and DMF (1 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (34.8 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.31-1.72 (8H, m), 1.74-2.01 (6H, m), 3.40-3.82 (6H, m), 3.98 (3H, s), 4.22 (3H, d, J = 5.8 Hz), 4.57 (1H, d, J = 3.8 Hz), 6.73-7.59 (8H, m), 8.12-8.25 (2H, m), 8.89 (1H, d, J = 2.3 Hz), 9.04 (2H, s).

Example 596

3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea

A) tert-butyl (trans-4-((benzylcarbamoyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)amino)cyclohexyl)carbamate

[0357] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate (2 g), (2-methoxypyrimidin-5-yl)boronic acid (1.221 g), PdCl₂(dppf) (0.29 g), 2 M sodium carbonate aqueous solution (3.96 mL) and DME (20 mL) was stirred under a nitrogen atmosphere at 80°C for 2 hr. The solvent of the reaction mixture was evaporated under reduced pressure, water was added at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.86 g).

MS: [M+H]⁺ 534.3.

B) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl) urea

[0358] A mixture of tert-butyl (trans-4-((benzylcarbamoyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)amino)cyclohexyl)carbamate (1.86 g) and TFA (10 mL) was stirred at room temperature for 20 min. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.26 g).

MS: [M+H]⁺ 434.2.

C) 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile

[0359] To a mixture of 2,4-dichloropyrimidine-5-carbonitrile (2.22 g), DIPEA (6.7 mL) and THF (30 mL) was added a mixture of azepan-4-ol hydrochloride (1.93 g) and DMF (10 mL) at 0°C. The reaction mixture was stirred at 0°C for 40 min, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether, and the crystal was filtered off. The obtained filtrate was concentrated, and the residue was purified by HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium acetate-based)). The obtained fraction was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (971 mg).

MS: [M+H]⁺ 253.1.

D) 3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea

[0360] A mixture of DIPEA (0.07 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea (50 mg), 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile (35 mg) and DMF (1 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate to give the title compound (71 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.31-2.17 (14H, m), 3.53-3.85 (6H, m), 3.97 (3H, s), 4.40 (2H, d, J = 5.9 Hz), 4.47-4.64 (2H, m), 7.19-7.63 (6H, m), 8.13-8.30 (1H, m), 8.93-9.03 (4H, m), 9.05-9.17 (1H, m).

Example 599

benzyl (trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0361] A mixture of DIPEA (0.081 mL), benzyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (50 mg), 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile (32.1 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl ace-

tate/hexane/methanol) to give the title compound (29.1 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.48 (2H, m), 1.48-1.70 (6H, m), 1.80-2.00 (6H, m), 3.38-3.79 (6H, m), 3.98 (3H, s), 4.01-4.20 (1H, m), 4.57 (1H, d, J = 3.87 Hz), 5.12 (2H, s), 7.25-7.61 (7H, m), 8.14-8.25 (2H, m), 8.88 (1H, d, J = 3.59 Hz), 9.04 (2H, s).

5 Example 600

benzyl (trans-4-((4-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

10 A) (1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-fluoroazetidin-3-yl)methanol

[0362] To a mixture of (3-fluoroazetidin-3-yl)methanol (500 mg), DIPEA (1.69 mL) and THF (30 mL) was added a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (1.053 g) and acetonitrile (30 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (371 mg). MS: [M+H]⁺ 286.0.

20 B) benzyl (trans-4-((4-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0363] A mixture of DIPEA (0.09 mL), benzyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (55.6 mg), (1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-fluoroazetidin-3-yl)methanol (36.6 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (18 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.27-1.47 (2H, m), 1.49-1.67 (2H, m), 1.80-2.04 (4H, m), 3.46-3.75 (3H, m), 3.98 (3H, s), 4.00-4.13 (3H, m), 4.24 (2H, dd, J = 19.17, 10.76 Hz), 5.12 (2H, s), 5.30-5.37 (1H, m), 7.22-7.48 (7H, m), 8.06-8.16 (1H, m), 8.23 (1H, d, J = 5.67 Hz), 8.86-8.91 (1H, m), 9.05 (2H, s).

30 Example 603

benzyl (trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-azetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

35 A) 2-chloro-4-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyrimidine-5-carbonitrile

[0364] To a mixture of (3-fluoroazetidin-3-yl)methanol (500 mg), DIPEA (1.69 mL) and THF (10 mL) was added a mixture of 2,4-dichloropyrimidine-5-carbonitrile (845 mg) and acetonitrile (30 mL) at room temperature. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (187 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 3.75 (2H, dd, J = 21.1, 6.0 Hz), 4.12-4.88 (4H, m), 5.39 (1H, t, J = 6.0 Hz), 8.63 (1H, s).

45 B) benzyl (trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-azetidine-1-yl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0365] A mixture of DIPEA (0.084 mL), benzyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (52 mg), 2-chloro-4-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyrimidine-5-carbonitrile (29.1 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (24.5 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.22-1.45 (2H, m), 1.45-1.69 (2H, m), 1.78-2.00 (4H, m), 3.44-3.77 (3H, m), 3.98 (3H, s), 4.03-4.40 (5H, m), 5.11 (2H, s), 5.31-5.37 (1H, m), 7.25-7.38 (5H, m), 7.45 (1H, dd, J = 8.26, 6.09 Hz), 7.62 (1H, dd, J = 17.99, 7.70 Hz), 8.18-8.26 (2H, m), 8.88 (1H, dd, J = 6.99, 2.45 Hz), 9.04 (2H, d, J = 3.21 Hz).

Example 605

3-benzyl-1-(trans-4-((5-cyano-4-((3-methyloxetan-3-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea

[0366] A mixture of DIPEA (0.071 mL), 3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea (73.1 mg), 3-methyloxetan-3-amine (14.1 mg) and DMF (1 mL) was stirred at room temperature overnight, and at 60°C for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (62.1 mg).

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22-1.50 (4H, m), 1.52-1.60 (3H, m), 1.74-1.91 (4H, m), 3.21-3.42 (1H, m), 3.88 (3H, s), 4.10-4.33 (5H, m), 4.58-4.72 (2H, m), 6.43-6.58 (1H, m), 7.14-7.63 (7H, m), 7.69-7.90 (1H, m), 7.96-8.04 (2H, m), 8.12-8.19 (1H, m), 8.27 (1H, s), 8.76 (1H, d, *J* = 2.0 Hz).

Example 606

3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

A) 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine

[0367] To a mixture of oxetan-3-ol (1.88 g) and THF (100 mL) was added sodium hydride (60% oil dispersion, 1.133 g) at 0°C. The mixture was stirred under a nitrogen atmosphere at 0°C for 30 min, and added to a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (5.23 g) and THF (10 mL) at 0°C. The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. To the reaction mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (782.7 mg).

MS: [M+H]⁺ 255.0.

B) 3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0368] A mixture of DIPEA (0.161 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea (100 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (58.7 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH₄ ethyl acetate/hexane/methanol) to give the title compound (45.8 mg). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.30-1.50 (2H, m), 1.77-2.01 (4H, m), 2.04-2.20 (2H, m), 3.43-3.88 (1H, m), 3.97 (3H, s), 4.41 (2H, d, *J* = 5.85 Hz), 4.50-4.67 (3H, m), 4.82-4.91 (2H, m), 5.64 (1H, dt, *J* = 18.55, 5.83 Hz), 7.15-7.43 (5H, m), 7.72-8.09 (1H, m), 8.34-8.47 (1H, m), 8.95-9.05 (4H, m), 9.06-9.17 (1H, m).

Example 608

benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

A) benzyl (5-bromopyrimidin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate

[0369] A mixture of 4-nitrophenyl (5-bromopyrimidin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate (22.7 g), phenylmethanol (18.3 g), potassium carbonate (20.4 g) and DMF (80 mL) was stirred under a nitrogen atmosphere at 90°C for 7 hr. Insoluble material was filtered off, water was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and treated with diisopropyl ether to give the title compound (16.2 g).

MS: [M+H]⁺ 505.1.

B) benzyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

[0370] A mixture of benzyl (5-bromopyrimidin-2-yl) (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbamate (8 g), (2-methoxypyrimidin-5-yl)boronic acid (4.87 g), PdCl₂(dppf) (1.15 g), 2 M sodium carbonate aqueous solution (30 mL) and DME (100 mL) was stirred under a nitrogen atmosphere at 90°C for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and treated with ethyl acetate and diisopropyl ether to give the title compound (5.47 g).

MS: [M+H]⁺ 535.1.

C) benzyl (trans-4-aminocyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

[0371] To a mixture of benzyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate (5.2 g) and acetonitrile (10 mL) was added dropwise TFA (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hr, and the solvent was evaporated under reduced pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate and THF. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (1.51 g).

MS: [M+H]⁺ 435.3.

D) benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

[0372] A mixture of DIPEA (0.07 mL), benzyl (trans-4-aminocyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate (50 mg), 2-chloro-4-(oxetan-3-ylamino)pyrimidine-5-carbonitrile (35 mg) and DMF (1 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate to give the title compound (59.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.48 (2H, m), 1.56-1.78 (2H, m), 1.81-1.97 (4H, m), 3.41-3.73 (1H, m), 3.99 (3H, s), 4.08-4.20 (1H, m), 4.55-4.72 (4H, m), 4.77-5.02 (1H, m), 5.15 (2H, s), 7.24-7.68 (6H, m), 7.96-8.12 (1H, m), 8.14-8.26 (1H, m), 9.08-9.14 (2H, m), 9.20-9.29 (2H, m).

Example 609

3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-yloxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0373] A mixture of DIPEA (0.162 mL), benzyl (trans-4-aminocyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate (100 mg), 2-chloro-4-(oxetan-3-yloxy)pyrimidine-5-carbonitrile (48.9 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (21.2 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.34-1.50 (2H, m), 1.50-1.67 (2H, m), 1.76-1.93 (4H, m), 3.39-3.71 (1H, m), 3.98 (3H, s), 4.15-4.29 (3H, m), 4.55-4.66 (2H, m), 4.72-4.89 (2H, m), 5.53-5.63 (1H, m), 6.81 (1H, dt, J = 18.81, 5.98 Hz), 7.18-7.36 (6H, m), 8.00-8.37 (2H, m), 8.48-8.53 (1H, m), 8.90 (1H, dd, J = 3.60 Hz), 9.04 (2H, d, J = 2.74 Hz).

Example 610

1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(pyridin-2-ylmethyl)urea

A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)((pyridin-2-ylmethyl)carbamoyl)amino)cyclohexyl)carbamate

[0374] A mixture of 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (720 mg), 1-(pyridin-2-yl)methanamine (414 mg) and NMP (15 mL) was stirred at 70°C overnight. To

the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, hexane/ethyl acetate/methanol) to give the title compound (681 mg).
MS: [M+H]⁺ 534.3.

B) 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl)urea

[0375] A mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)((pyridin-2-ylmethyl)carbamoyl)amino)cyclohexyl)carbamate (681 mg) and TFA (10 mL) was stirred at room temperature for 2 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, hexane/ethyl acetate/methanol) to give the title compound (486 mg).
MS: [M+H]⁺ 434.2.

C) 1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(pyridin-2-ylmethyl)urea

[0376] A mixture of DIPEA (0.135 mL), 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl)urea (84 mg), 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile (52.4 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (75.4 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.70 (4H, m), 1.80-1.95 (4H, m), 3.40-3.75 (1H, m), 3.99 (3H, s), 4.16-4.36 (3H, m), 4.51-4.61 (2H, m), 4.75-4.89 (2H, m), 5.54-5.64 (1H, m), 6.82-6.92 (1H, m), 7.22 (1H, t, J = 6.23 Hz), 7.30 (1H, d, J = 7.93 Hz), 7.44 (1H, dd, J = 8.31, 5.67 Hz), 7.73-8.08 (2H, m), 8.25 (1H, td, J = 7.60, 2.55 Hz), 8.33 (1H, d, J = 4.91 Hz), 8.46 (1H, d, J = 4.91 Hz), 8.93 (1H, dd, J = 5.29, 2.55 Hz), 9.06 (2H, d, J = 2.36 Hz).

Example 611

benzyl (trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

[0377] A mixture of DIPEA (0.07 mL), benzyl (trans-4-aminocyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate (50 mg), 2-chloro-4-(4-hydroxyazepan-1-yl)pyrimidine-5-carbonitrile (32 mg) and DMF (1 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (29.2 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 1.40 (2H, brs), 1.64 (5H, brs), 1.80-1.99 (6H, m), 3.44-3.84 (7H, m), 3.99 (3H, s), 4.13 (1H, brs), 4.58 (1H, brs), 5.15 (2H, brs), 7.25-7.58 (6H, m), 8.11-8.25 (1H, m), 9.11 (2H, s), 9.24 (2H, brs).

Example 612

3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0378] A mixture of tert-butyl (trans-4-((5-bromopyrazin-2-yl)amino)cyclohexyl)carbamate (1.5 g), (2-methoxypyrimidin-5-yl)boronic acid (0.933 g), PdCl₂(dppf) (0.302 g), 2 M cesium carbonate aqueous solution (5.05 mL) and DME (20 mL) was stirred under a nitrogen atmosphere at 90°C for 2 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate and THF. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.41 g).
MS: [M+H]⁺ 401.2.

B) 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0379] A mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (500 mg), 4-nitrophenyl carbonochloridate (755 mg), DIPEA (1.308 mL) and THF (50 mL) was stirred at 70°C for 5 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (412 mg).

MS: $[M+H]^+$ 566.2.

C) tert-butyl (trans-4-((benzylcarbamoyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0380] A mixture of 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (420 mg), 1-phenylmethanamine (0.244 mL) and NMP (10 mL) was stirred at 70°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (340 mg). MS: $[M+H]^+$ 534.3.

D) 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0381] A mixture of tert-butyl (trans-4-((benzylcarbamoyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (340 mg) and TFA (10 mL) was stirred at room temperature for 3 hr, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (220 mg). MS: $[M+H]^+$ 434.2.

E) 3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0382] A mixture of DIPEA (0.101 mL), 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (50 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (32.3 mg) and DMF (2 mL) was stirred at 70°C for 2 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (10 mg). 1H NMR (300 MHz, DMSO- d_6) δ 1.32-1.47 (2H, m), 1.47-1.66 (2H, m), 1.78-1.98 (4H, m), 3.22-3.70 (1H, m), 4.01 (3H, s), 4.20-4.33 (3H, m), 4.51-4.62 (2H, m), 4.76-4.90 (2H, m), 5.54-5.64 (1H, m), 7.11-7.35 (6H, m), 7.70-8.06 (1H, m), 8.33 (1H, d, J = 5.10 Hz), 8.58 (1H, dd, J = 7.18, 1.32 Hz), 9.22 (1H, d, J = 6.83 Hz), 9.32 (2H, d, J = 5.29 Hz).

Example 614

3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea

A) 2-chloro-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidine-5-carbonitrile

[0383] A mixture of 2,4-dichloropyrimidine-5-carbonitrile (0.54 g), 3-methylazetidin-3-ol hydrochloride (0.422 g), DIPEA (1.084 mL) and THF (10 mL) was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (0.32 g). MS: $[M+H]^+$ 225.1.

B) 3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea

[0384] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea (64.4 mg), 2-chloro-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidine-5-carbonitrile (36.7 mg), DIPEA (0.13 mL) and DMF (1 mL) was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (41.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.29-1.50 (5H, m), 1.71-2.24 (6H, m), 3.55-3.88 (1H, m), 3.93-4.18 (7H, m), 4.40 (2H, d, J = 5.9 Hz), 4.46-4.61 (1H, m), 5.71 (1H, d, J = 2.0 Hz), 7.20-7.45 (5H, m), 7.49-7.65 (1H, m), 8.13-8.30 (1H, m), 8.95-9.01 (4H, m), 9.05-9.18 (1H, m).

5 Example 617

3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

10 A) 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol

[0385] To a mixture of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (843 mg), DIPEA (2.5 mL), DMF (5 mL) and THF (5 mL) was added 3-methylazetidin-3-ol hydrochloride (480 mg) at room temperature. The reaction mixture was stirred at room temperature for 2 hr, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (722 mg).

MS: [M+H]⁺ 268.1.

20 B) 3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0386] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (48.4 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (32.9 mg), DIPEA (0.097 mL) and DMF (1 mL) was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (14.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.65 (7H, m), 1.75-2.04 (4H, m), 3.40-3.70 (1H, m), 3.93 (4H, s), 4.01 (3H, s), 4.19-4.34 (3H, m), 5.58-5.66 (1H, m), 7.10-7.38 (7H, m), 8.01-8.11 (1H, m), 8.57 (1H, s), 9.18-9.26 (1H, m), 9.32 (2H, s).

Example 618

3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea

[0387] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea trifluoroacetate (60.5 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (32.6 mg), DIPEA (0.102 mL) and DMF (1 mL) was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (18.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.32-1.47 (4H, m), 1.76-1.97 (4H, m), 3.34-3.69 (1H, m), 3.92 (3H, s), 4.15-4.29 (3H, m), 4.50-4.63 (2H, m), 4.71-4.91 (2H, m), 5.52-5.64 (1H, m), 6.76-6.85 (1H, m), 7.16-7.35 (5H, m), 7.69-8.03 (1H, m), 8.08-8.15 (1H, m), 8.31 (1H, s), 8.38-8.45 (2H, m), 8.85-8.94 (1H, m).

Example 619

benzyl (trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate

[0388] A mixture of benzyl (trans-4-aminocyclohexyl) (2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate (80 mg), 2-chloro-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidine-5-carbonitrile (50 mg), DIPEA (0.15 mL) and DMF (1.5 mL) was stirred at room temperature overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH₄OH, ethyl acetate/hexane) and crystallized from ethyl acetate to give the title compound (96 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.31-1.46 (5H, m), 1.67 (2H, brs), 1.79-1.99 (4H, m), 3.45-3.73 (1H, m), 3.89-4.20 (8H,

m), 5.15 (2H, s), 5.69 (1H, d, J = 4.2 Hz), 7.26-7.39 (5H, m), 7.47-7.62 (1H, m), 8.11-8.26 (1H, m), 9.11 (2H, d, J = 3.1 Hz), 9.24 (2H, d, J = 6.0 Hz) .

Example 620

3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0389] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (66.3 mg), 2-chloro-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidine-5-carbonitrile (37.8 mg), DIPEA (0.134 mL) and DMF (1 mL) was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (65.5 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.64 (7H, m), 1.72-2.00 (4H, m), 3.41-3.72 (1H, m), 3.88-4.15 (7H, m), 4.18-4.33 (3H, m), 5.68 (1H, d, J = 8.6 Hz), 7.08-7.36 (6H, m), 7.56 (1H, dd, J = 19.0, 7.9 Hz), 8.17 (1H, d, J = 19.9 Hz), 8.57 (1H, dd, J = 3.9, 1.4 Hz), 9.21 (1H, dd, J = 7.1, 1.3 Hz), 9.31 (2H, d, J = 4.6 Hz) .

Example 623

N-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide

[0390] A mixture of N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide (50 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (37 mg), DIPEA (0.1 mL) and DMF (1 mL) was stirred at 70°C for 4 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (21.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.29-1.48 (7H, m), 1.79-2.03 (4H, m), 3.41-3.64 (1H, m), 3.92 (4H, brs), 3.99 (3H, s), 4.26-4.51 (3H, m), 5.61 (1H, d, J = 7.6 Hz), 6.75 (2H, d, J = 8.1 Hz), 6.91 (1H, t, J = 7.2 Hz), 7.09-7.31 (3H, m), 7.57-7.70 (1H, m), 8.06 (1H, d, J = 7.5 Hz), 8.28-8.40 (1H, m), 8.94-9.03 (1H, m), 9.08 (2H, brs).

Example 625

3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0391] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (60 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (37.1 mg), DIPEA (71.7 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium bicarbonate-based)) to give the title compound (11.5 mg) .

¹H NMR (300 MHz, DMSO-d₆) δ 1.32-1.44 (5H, m), 1.45-1.61 (2H, m), 1.75-1.89 (3H, m), 1.91-2.00 (1H, m), 3.42-3.66 (1H, m), 3.90-3.93 (4H, m), 3.98 (3H, s), 4.17-4.26 (3H, m), 5.62 (1H, d, J = 5.38 Hz), 6.80 (1H, s), 7.13-7.35 (7H, m), 8.07 (1H, d, J = 13.88 Hz), 8.20 (1H, brs), 8.90 (1H, brs), 9.05 (2H, s).

Example 626

3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0392] A mixture of 1-(trans-4-aminocyclohexyl)-3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (60 mg), 2-chloro-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidine-5-carbonitrile (31.2 mg), DIPEA (71.7 mg) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (13.53 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.23-1.61 (7H, m), 1.72-1.86 (3H, m), 1.86-1.98 (1H, m), 3.37-3.67 (1H, m), 3.91-4.27

(10H, m), 5.68 (1H, d, J = 8.69 Hz), 6.75-6.83 (1H, m), 7.17-7.34 (6H, m), 7.54 (1H, dd, J = 18.65, 7.98 Hz), 8.13-8.24 (2H, m), 8.89 (1H, dd, J = 6.80, 2.27 Hz), 9.04 (2H, d, J = 3.87 Hz).

Example 627

N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-N-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-phenoxyacetamide

[0393] A mixture of N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide (100 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (70.5 mg), DIPEA (0.2 mL) and DMF (2 mL) was stirred at 70°C for 4 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (84.9 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.29-1.56 (4H, m), 1.77-1.98 (4H, m), 3.36-3.68 (1H, m), 3.99 (3H, s), 4.26-4.48 (3H, m), 4.49-4.63 (2H, m), 4.72-4.91 (2H, m), 5.52-5.64 (1H, m), 6.75 (2H, d, J = 8.1 Hz), 6.91 (1H, t, J = 7.3 Hz), 7.24 (2H, t, J = 7.9 Hz), 7.57-7.69 (1H, m), 7.72-8.04 (1H, m), 8.28-8.42 (2H, m), 8.99 (1H, dd, J = 10.5, 2.2 Hz), 9.06-9.11 (2H, m).

Example 628

pyridin-2-ylmethyl (trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

A) pyridin-2-ylmethyl (trans-4-aminocyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0394] To a mixture of pyridin-2-ylmethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (655 mg) and acetonitrile (3 mL) was added TFA (1.5 mL) at room temperature, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (487 mg).

MS: [M+H]⁺ 435.2.

B) pyridin-2-ylmethyl (trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0395] A mixture of pyridin-2-ylmethyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (100 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (73.9 mg), DIPEA (0.2 mL) and DMF (2 mL) was stirred 70°C for 4 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound (86.6 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.47 (5H, m), 1.50-1.72 (2H, m), 1.80-2.06 (4H, m), 3.42-3.70 (1H, m), 3.93 (4H, s), 3.97-4.14 (4H, m), 5.17 (2H, s), 5.62 (1H, brs), 7.08-7.36 (3H, m), 7.48-7.60 (1H, m), 7.80 (1H, t, J = 6.9 Hz), 8.07 (1H, d, J = 15.0 Hz), 8.19-8.30 (1H, m), 8.53 (1H, d, J = 4.2 Hz), 8.85-8.96 (1H, m), 9.06 (2H, s).

Example 629

pyridin-2-ylmethyl (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)carbamate

[0396] A mixture of pyridin-2-ylmethyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (100 mg), 2-chloro-4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidine (70.3 mg), DIPEA (0.2 mL) and DMF (2 mL) was stirred at 70°C for 4 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate and diisopropyl ether to give the title compound

(122 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.50 (2H, m), 1.51-1.77 (2H, m), 1.85-2.02 (4H, m), 3.38-3.70 (1H, m), 3.98 (3H, s), 4.04-4.22 (1H, m), 4.49-4.64 (2H, m), 4.73-4.92 (2H, m), 5.17 (2H, s), 5.52-5.65 (1H, m), 7.22-7.36 (2H, m), 7.50-7.61 (1H, m), 7.72-8.04 (2H, m), 8.25 (1H, td, J = 8.1, 2.5 Hz), 8.34 (1H, d, J = 6.4 Hz), 8.53 (1H, d, J = 4.5 Hz), 8.91 (1H, dd, J = 8.1, 2.5 Hz), 9.01-9.10 (2H, m).

Example 630

1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxy-
ypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl)urea

[0397] A mixture of 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl)urea (114 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (84.2 mg), DIPEA (0.183 mL) and DMF (2 mL) was stirred at 70°C overnight. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (77 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.33-1.44 (5H, m), 1.46-1.63 (2H, m), 1.84 (3H, brs), 1.89-2.02 (1H, m), 3.40-3.67 (1H, m), 3.93 (4H, s), 3.99 (3H, s), 4.23 (1H, brs), 4.31 (2H, d, J = 5.38 Hz), 5.62 (1H, d, J = 4.15 Hz), 6.85 (1H, t, J = 5.74 Hz), 7.03-7.31 (3H, m), 7.43 (1H, d, J = 4.36 Hz), 7.76 (1H, t, J = 7.78 Hz), 8.07 (1H, d, J = 14.35 Hz), 8.24 (1H, brs), 8.45 (1H, d, J = 4.76 Hz), 8.93 (1H, brs), 9.06 (2H, s).

Example 631

1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxy-
ypyrimidin-5-yl)pyridin-2-yl)-3-((1R)-1-phenylethyl)urea

A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl))((1R)-1-phenylethyl)carbamoyl)amino)cyclohexyl)carbamate

[0398] A mixture of (1R)-1-phenylethylamine (455 mg), 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (706 mg) and NMP (25 mL) was stirred at 70°C for 18 hr and at 100°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (617 mg).

MS: [M+H]⁺ 547.3.

B) 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1R)-1-phenylethyl)urea

[0399] A mixture of TFA (5 mL) and tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl))((1R)-1-phenylethyl)carbamoyl)amino)cyclohexyl)carbamate (617 mg) was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (480 mg).

MS: [M+H]⁺ 447.2.

C) 1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxy-
ypyrimidin-5-yl)pyridin-2-yl)-3-((1R)-1-phenylethyl)urea

[0400] A mixture of 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1R)-1-phenylethyl)urea (116 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (76 mg), DIPEA (0.181 mL) and DMF (2 mL) was stirred at 70°C for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and HPLC (water/acetonitrile (5 mM ammonium bicarbonate-based)) to give the title compound (60.3 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.27-1.44 (8H, m), 1.49-1.71 (2H, m), 1.71-2.00 (4H, m), 3.40-3.69 (1H, m), 3.93 (4H, s), 3.98 (3H, s), 4.22 (1H, brs), 4.91 (1H, t, J = 7.55 Hz), 5.62 (1H, brs), 6.87-7.04 (1H, m), 7.08-7.33 (7H, m), 8.03-8.20 (2H, m), 8.86 (1H, d, J = 2.36 Hz), 9.04 (2H, s).

Example 633

1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1S)-1-phenylethyl)urea

A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl))((1S)-1-phenylethyl)carbamoyl)amino)cyclohexyl)carbamate

[0401] A mixture of (1S)-1-phenylethylamine (455 mg), 4-nitrophenyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (706 mg) and NMP (25 mL) was stirred at 70°C for 18 hr and at 100°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (617 mg).

MS: [M+H]⁺ 547.3.

B) 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1S)-1-phenylethyl)urea

[0402] A mixture of TFA (5 mL) and tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl))((1S)-1-phenylethyl)carbamoyl)amino)cyclohexyl)carbamate (617 mg) was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (484 mg).

MS: [M+H]⁺ 447.2.

C) 1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1S)-1-phenylethyl)urea

[0403] A mixture of 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1S)-1-phenylethyl)urea (118 mg), 1-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-3-methylazetidin-3-ol (78 mg), DIPEA (0.185 mL) and DMF (2 mL) was stirred at room temperature for 18 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and HPLC (L-Column 2 ODS, mobile phase: water/acetonitrile (5 mM ammonium bicarbonate-based)) to give the title compound (50.3 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-1.43 (8H, m), 1.51-2.02 (6H, m), 3.41-3.66 (1H, m), 3.93 (4H, s), 3.98 (3H, s), 4.23 (1H, brs), 4.86-4.96 (1H, m), 5.62 (1H, brs), 6.87-7.02 (1H, m), 7.11-7.34 (7H, m), 8.07 (1H, d, J = 16.24 Hz), 8.17 (1H, d, J = 4.38 Hz), 8.86 (1H, s), 9.04 (2H, s).

Example 693

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea A) tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

[0404] A mixture of tert-butyl (trans-4-((5-bromopyridin-2-yl)amino)cyclohexyl)carbamate (5.0 g), (2-methoxypyrimidin-5-yl)boronic acid (2.5 g), PdCl₂(dppf) (0.494 g), 2 M sodium carbonate aqueous solution (13.5 mL) and DME (52 mL) was stirred with heating under reflux under a nitrogen atmosphere for 2.5 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by isopropanol/ethyl acetate to give the title compound (3.23 g). MS: [M+H]⁺ 400.2.

B) tert-butyl (trans-4-(3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)ureido)cyclohexyl)carbamate

[0405] A mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (1.36 g), triphosgene (505 mg), DIPEA (1.3 g) and THF (25 mL) was stirred at 70°C for 30 min. 2,2-difluoroethane-1-amine (1.4 g) was added to the reaction mixture, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.42 g).

MS: [M+H]⁺ 507.3.

C) 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0406] A mixture of tert-butyl (trans-4-(3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)ureido)cyclohexyl)carbamate (1.429 g) and TFA (4.3 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (1.07 g). MS: $[M+H]^+$ 407.3.

D) 4-chloro-2-(methylthio)-5-(trifluoromethyl)pyrimidine

[0407] To a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (7.52 g) in THF (110 mL) was added dropwise 2 M zinc chloride · 2-methyltetrahydrofuran solution (20.8 mL) at 0°C, and the mixture was stirred while allowing to return to room temperature for 2 hr. To the reaction mixture was added sodium methanethiolate (2.7 g), and the mixture was stirred at room temperature for 16 hr. To the reaction mixture was added 2M hydrochloric acid at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (5.25 g). MS: $[M+H]^+$ 229.0.

E) 2-(methylthio)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-5-(trifluoromethyl)pyrimidine

[0408] A mixture of 4-chloro-2-(methylthio)-5-(trifluoromethyl)pyrimidine (7.44 g), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10.9 g), $\text{PdCl}_2(\text{Amphos})_2$ (1.6 g), 3 M sodium carbonate (21 mL) and DME (84 mL) was stirred under a nitrogen atmosphere at 100°C for 1.5 hr. The mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (8.6 g). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.40-1.52 (2H, m), 1.54-1.66 (1H, m), 1.86-2.00 (2H, m), 2.21-2.35 (1H, m), 2.60 (3H, s), 3.33-3.41 (1H, m), 3.62 (1H, dt, $J = 11.1, 3.7$ Hz), 5.67 (1H, dd, $J = 8.3, 2.7$ Hz), 6.65 (1H, dd, $J = 2.0, 1.0$ Hz), 7.67 (1H, d, $J = 2.0$ Hz), 9.12 (1H, s).

F) 2-(methylthio)-4-(1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine

[0409] A mixture of 2-(methylthio)-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-5-(trifluoromethyl)pyrimidine (7.03 g), 6 M aqueous hydrochloric acid solution (10 mL) and MeOH (70 mL) was stirred at room temperature for 1 hr. The reaction mixture was stirred at 0°C for 30 min, and the precipitated solid was collected by filtration and washed with cold methanol to give the title compound (4.55 g). MS: $[M+H]^+$ 261.1.

G) 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine

[0410] To a solution of 2-(methylthio)-4-(1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (5.24 g) in acetonitrile (150 mL) was added sulfuryl chloride (8.1 mL) at 0°C, and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.3 g). MS: $[M+H]^+$ 283.0.

H) 2-chloro-4-(4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine

[0411] A mixture of 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (1.00 g), 3,4-dihydro-2H-pyran (0.48 mL), TFA (0.27 mL) and toluene (20 mL) was stirred at 80°C for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.295 g). MS: $[M+H]^+$ 367.0.

l) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

[0412] A mixture of 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea (70 mg), 2-chloro-4-(4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (97 mg), DIPEA (0.15 mL) and acetonitrile (2 mL) was stirred at 80°C for 4 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL), and 6 M aqueous hydrochloric acid solution (0.20 mL) was added at room temperature. The mixture was stirred at 60°C for 2 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and treated with ethyl acetate and hexane to give the title compound (59 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.68 (4H, m), 1.73-2.08 (4H, m), 3.25-3.50 (2H, m), 3.51-3.79 (1H, m), 3.92-4.05 (3H, m), 4.12-4.33 (1H, m), 5.71-6.24 (1H, m), 6.46-6.69 (1H, m), 7.23-7.43 (1H, m), 8.00-8.18 (2H, m), 8.18-8.28 (1H, m), 8.58-8.69 (1H, m), 8.86-8.94 (1H, m), 9.01-9.10 (2H, m), 13.33-13.66 (1H, m).

Example 729

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea

A) tert-butyl (trans-4-((chlorocarbonyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate

[0413] To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (1.6 g) and DIPEA (2.1 mL) in THF (50 mL) was added triphosgene (594 mg) at room temperature. The reaction mixture was stirred at 60°C for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.75 g). MS: [M+H-tBu]⁺ 406.1.

B) tert-butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)ureido)cyclohexyl)carbamate

[0414] A mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (100 mg), 2,2,2-trifluoroethane-1-amine (64 mg), TEA (0.091 mL) and THF (2 mL) was stirred under microwave irradiation at 70°C for 2 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (112 mg). MS: [M+H]⁺ 525.3.

C) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea

[0415] tert-Butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)ureido)cyclohexyl)carbamate (100 mg) was dissolved in TFA (1 mL) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile (3 mL), and 2-chloro-4-(4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (108 mg) and DIPEA (0.33 mL) were added at room temperature. The mixture was stirred at 80°C for 4 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL), and 6 M aqueous hydrochloric acid solution (0.20 mL) was added at room temperature. The mixture was stirred at 60°C for 2 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and treated with ethyl acetate and hexane to give the title compound (55 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.31-1.65 (4H, m), 1.71-2.07 (4H, m), 3.52-3.89 (3H, m), 3.92-4.05 (3H, m), 4.14-4.33 (1H, m), 6.68-6.85 (1H, m), 7.24-7.38 (1H, m), 8.01-8.18 (2H, m), 8.19-8.31 (1H, m), 8.57-8.69 (1H, m), 8.86-8.98 (1H, m), 9.00-9.12 (2H, m), 13.35-13.63 (1H, m).

Example 740

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoropropyl)-
1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea A) tert-butyl (trans-4-((chlorocarbonyl) (5-(2-methoxypyrimidin-5-
yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0416] To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (3.0 g) and DIPEA (2.9 g) in THF (50 mL) was added triphosgene (1.1 g) at room temperature. The reaction mixture was stirred at 60°C for 1 hr. To the reaction mixture were added DIPEA (2.9 g) and triphosgene (778 mg), and the mixture was stirred at 75°C for 1 hr. The reaction mixture was added to ice water, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.1 g). MS: [M+H-tBu]⁺ 407.2.

B) tert-butyl (trans-4-(3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0417] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (400 mg) and 2,2-difluoropropane-1-amine hydrochloride (182 mg) in THF (5 mL) was added DIPEA (391 mg) at room temperature. The reaction mixture was stirred at 75°C for 1 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the obtained solid was washed with diisopropyl ether to give the title compound (370 mg). MS: [M+H]⁺ 522.3.

C) 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0418] A mixture of tert-butyl (trans-4-(3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate (388 mg) and TFA (5 mL) was stirred at room temperature overnight. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (300 mg). MS: [M+H]⁺ 422.3.

D) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0419] To a solution of 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (50 mg) and 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (50 mg) in DMF (2.0 mL) was added DIPEA (0.06 mL) at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by HPLC (YMCTriartC18, mobile phase: water/acetonitrile (10 mM ammonium bicarbonate-based)) to give the title compound (22 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.33-1.68 (7H, m), 1.74-1.88 (2H, m), 1.90-2.04 (2H, m), 3.38-3.57 (2H, m), 3.57-3.81 (1H, m), 4.01 (3H, d, J = 2.3 Hz), 4.21-4.37 (1H, m), 6.98-7.11 (1H, m), 7.97-8.26 (2H, m), 8.49-8.58 (1H, m), 8.59-8.70 (1H, m), 9.21 (1H, dd, J = 4.9, 1.1 Hz), 9.32 (2H, d, J = 6.0 Hz), 13.48 (1H, br d, J = 4.2 Hz).

Example 742

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-((1-fluorocyclopropyl)methyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

A) tert-butyl (trans-4-(3-((1-fluorocyclopropyl)methyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0420] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (50 mg) and (1-fluorocyclopropyl)methanamine hydrochloride (16 mg) in THF (2.0 mL) was added DIPEA (0.056 mL) at room temperature, and the reaction mixture was stirred at room temperature for 2 hr. To the reaction

mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (48 mg).

MS: $[M+H]^+$ 516.3.

B) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-((1-fluorocyclopropyl)methyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0421] tert-Butyl (trans-4-(3-((1-fluorocyclopropyl)methyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate (48 mg) was dissolved in TFA (3.0 mL) at room temperature, and the mixture was stirred at room temperature for 1 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was dissolved in DMF (3.0 mL), and 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (40 mg) and DIPEA (0.32 mL) were added at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) and HPLC (YMCTriartC18, mobile phase: water/acetonitrile (10 mM ammonium bicarbonate-based)) to give the title compound (12 mg).

¹H NMR (300 MHz, DMSO-*d*₆) δ 0.62-0.80 (2H, m), 0.85-1.04 (2H, m), 1.33-1.72 (4H, m), 1.72-1.87 (2H, m), 1.89-2.05 (2H, m), 3.41-3.56 (2H, m), 3.58-3.80 (1H, m), 4.01 (3H, d, *J* = 2.3 Hz), 4.20-4.39 (1H, m), 6.98-7.15 (1H, m), 7.98-8.23 (2H, m), 8.48-8.56 (1H, m), 8.59-8.71 (1H, m), 9.13-9.23 (1H, m), 9.30 (2H, d, *J* = 6.0 Hz), 13.48 (1H, br s).

Example 743

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea

A) tert-butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)ureido)cyclohexyl)carbamate

[0422] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (394 mg) and DIPEA (385 mg) in THF (5.0 mL) was added 2,2,2-trifluoroethane-1-amine hydrochloride (184 mg) at room temperature, and the reaction mixture was stirred at 70°C for 1 hr. The reaction mixture was added to ice water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The precipitated solid was collected by filtration, and the obtained solid was washed with diisopropyl ether to give the title compound (395 mg).

MS: $[M+H]^+$ 526.4.

B) 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea

[0423] A mixture of tert-butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)ureido)cyclohexyl)carbamate (388 mg) and TFA (4.0 mL) was stirred at room temperature overnight. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (320 mg).

MS: $[M+H]^+$ 426.2.

C) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea

[0424] A mixture of 1-(trans-4-aminocyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea (40 mg), 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (40 mg), DIPEA (0.03 mL) and DMF (1 mL) was stirred at 70°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (12 mg).

¹H NMR (300 MHz, DMSO-*d*₆) δ 1.35-1.63 (4H, m), 1.77-2.06 (4H, m), 3.65 (1H, br s), 3.73-3.91 (2H, m), 4.02 (3H, d, *J* = 2.3 Hz), 4.18-4.35 (1H, m), 7.07-7.19 (1H, m), 8.03-8.20 (2H, m), 8.55 (1H, dd, *J* = 5.7, 1.1 Hz), 8.59-8.70 (1H, m), 9.25 (1H, dd, *J* = 5.1, 1.3 Hz), 9.33 (2H, d, *J* = 6.0 Hz), 13.48 (1H, br s).

Example 744

1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea A) tert-butyl (trans-4-(3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0425] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (400 mg) and 2,2-difluoroethane-1-amine (112 mg) in THF (5.0 mL) was added DIPEA (0.223 mg) at room temperature, and the reaction mixture was stirred at 75°C for 1 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The precipitated solid was collected by filtration to give the title compound (392 mg).

B) 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0426] A mixture of tert-butyl (trans-4-(3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate (388 mg) and TFA (4.7 mL) was stirred at room temperature overnight. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (311 mg).

MS: [M+H]⁺ 408.2.

C) 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0427] To a solution of 1-(trans-4-aminocyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (100 mg) and 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (139 mg) in DMF (2.0 mL) was added DIPEA (0.13 mL) at room temperature. The reaction mixture was purified by HPLC (YMCTriartC18, mobile phase: water/acetonitrile (10 mM ammonium bicarbonate-based)) to give the title compound (33 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.63 (4H, m), 1.73-2.06 (4H, m), 3.35-3.50 (2H, m), 3.56-3.80 (1H, m), 4.02 (3H, d, J = 2.6 Hz), 4.17-4.36 (1H, m), 5.78-6.25 (1H, m), 6.89-7.05 (1H, m), 7.99-8.26 (2H, m), 8.57 (1H, dd, J = 5.5, 1.3 Hz), 8.64 (1H, d, J = 9.4 Hz), 9.23 (1H, dd, J = 4.9, 1.1 Hz), 9.32 (2H, d, J = 6.0 Hz), 13.49 (1H, br s).

Example 764

1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) urea

A) tert-butyl (trans-4-((chlorocarbonyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate

[0428] To a mixture of tert-butyl (trans-4-((5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (1.8 g) and DIPEA (1.9 g) in THF (40 mL) was added triphosgene (717 mg) at room temperature. The reaction mixture was stirred at 70°C for 1 hr. The reaction mixture was added to ice water, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.82 g). MS: [M+H-tBu]⁺ 379.2.

B) tert-butyl (trans-4-(3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0429] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (300 mg) and DIPEA (356 mg) in THF (5.0 mL) was added ethaneamine hydrochloride (79 mg) at room temperature, and the reaction mixture was stirred at 70°C for 3 hr. To the reaction mixture was added water and ethyl acetate at room temperature, and the precipitated solid was collected by filtration to give the title compound (250 mg). MS: [M+H]⁺ 444.3.

C) 1-(trans-4-aminocyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea

[0430] A mixture of tert-butyl (trans-4-(3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)ureido)cyclohexyl)car-

bamate (294 mg) and TFA (4.0 mL) was stirred at room temperature for 3 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol) to give the title compound (214 mg).

MS: [M+H]⁺ 344.2.

D) 1-(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

[0431] A mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5 g), sodium 2-chloro-2,2-difluoroacetate (4.71 g), 18-crown-6 (1.36 g) and acetonitrile (120 mL) was stirred at 80°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was washed with diisopropyl ether/hexane to give the title compound (2.2 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.29 (12H, s), 6.73 (1H, d, J = 2.6 Hz), 7.87 (1H, t, J = 59.1 Hz), 8.28 (1H, d, J = 2.6 Hz).

E) 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylthio)-5-(trifluoromethyl)pyrimidine

[0432] A mixture of 4-chloro-2-(methylthio)-5-(trifluoromethyl)pyrimidine (1.5 g), 1-(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.76 g), PdCl₂(Amphos)₂ (465 mg), 2M sodium carbonate aqueous solution (6.6 mL) and DME (30 mL) was stirred under an argon atmosphere at 100°C for 4 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.51 g). MS: [M+H]⁺ 311.0.

F) 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidine

[0433] A mixture of 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylthio)-5-(trifluoromethyl)pyrimidine (1 g), m-chloroperoxybenzoic acid (1.99 g) and ethyl acetate (30 mL) was stirred at room temperature overnight. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (825 mg).

MS: [M+H]⁺ 343.0.

G) 1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) urea

[0434] A mixture of 1-(trans-4-aminocyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea (141 mg), 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidine (155 mg), DIPEA (0.21 mL) and DMF (2 mL) was stirred at 70°C for 3 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, ethyl acetate/hexane and NH, ethyl acetate/hexane) to give the title compound (80 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (3H, t, J = 7.0 Hz), 1.33-1.54 (4H, m), 1.73-1.98 (4H, m), 2.96-3.11 (2H, m), 3.64 (1H, br s), 3.92 (3H, s), 4.21 (1H, br s), 6.25-6.37 (1H, m), 6.87 (1H, dd, J = 10.0, 2.8 Hz), 7.64-8.07 (1H, m), 8.02-8.18 (2H, m), 8.30-8.36 (2H, m), 8.39 (1H, s), 8.63 (1H, d, J = 7.2 Hz), 8.85 (1H, d, J = 1.1 Hz).

Example 766

2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

A) 2,2-difluoroethyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0435] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (300 mg), 2,2-difluoroethanol (160 mg) and DIPEA (0.34 mL) in THF (4.0 mL) was added DMAP

(95 mg) at room temperature, and the mixture was stirred at 60°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 2,2-difluoroethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (308 mg). 2,2-Difluoroethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (308 mg) was dissolved in TFA (3.0 mL), and the mixture was stirred at room temperature for 30 min. The solvent of the reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH₄OH, ethyl acetate/methanol) to give the title compound (212 mg).

MS: [M+H]⁺ 409.2.

B) 4-(5-(methylsulfonyl)pyridin-3-yl)-2-(methylthio)-5-(trifluoromethyl)pyrimidine

[0436] A mixture of 4-chloro-2-(methylthio)-5-(trifluoromethyl)pyrimidine (1.0 g), 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.3 g), PdCl₂(Amphos)₂ (310 mg), 2 M sodium carbonate aqueous solution (4.4 mL) and DME (10 mL) was stirred under microwave irradiation at 100°C for 1 hr. A similar reaction was repeated 6 times, to the combined reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (7.1 g).

MS: [M+H]⁺ 350.0.

C) 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine

[0437] To a solution of 4-(5-(methylsulfonyl)pyridin-3-yl)-2-(methylthio)-5-(trifluoromethyl)pyrimidine (7.1 g) in ethyl acetate (200 mL) was added m-chloroperbenzoic acid (11.0 g) at 0°C. After stirring at room temperature for 5 hr, the reaction solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (5.7 g).

MS: [M+H]⁺ 382.0.

D) 2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0438] To a solution of 2,2-difluoroethyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (81 mg) and 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (76 mg) in DMF (1.0 mL) was added DIPEA (0.1 mL) at room temperature, and the reaction mixture was stirred at 70°C for 3 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH₄OH, ethyl acetate/hexane and silica gel, ethyl acetate/hexane) to give the title compound (64 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.34-1.80 (4H, m), 1.85-2.09 (4H, m), 3.34-3.43 (3H, m), 3.56-3.86 (1H, m), 3.96-4.05 (3H, m), 4.08-4.23 (1H, m), 4.27-4.53 (2H, m), 5.93-6.51 (1H, m), 8.23 (1H, br d, J = 3.4 Hz), 8.38-8.50 (1H, m), 8.67-8.78 (2H, m), 9.01 (1H, s), 9.17-9.26 (2H, m), 9.27-9.34 (2H, m).

Example 767

2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

A) 2-(dimethylamino)ethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0439] A mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (200 mg), 2-(dimethylamino)ethanol (0.22 mL), DMAP (63.3 mg), TEA (0.18 mL) and THF (5 mL) was stirred at 70°C for 8 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH₄OH, ethyl acetate/hexane) to give the title compound (142 mg).

MS: [M+H]⁺ 516.4.

B) 2-(dimethylamino)ethyl (trans-4-aminocyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

5 **[0440]** A mixture of 2-(dimethylamino)ethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (142 mg) and TFA (2 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (105 mg). MS: [M+H]⁺ 416.2.

10 C) 2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

15 **[0441]** To a solution of 2-(dimethylamino)ethyl (trans-4-aminocyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (41 mg) and 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (38 mg) in DMF (2.0 mL) was added DIPEA (0.05 mL) at room temperature, and the mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol) to give the title compound (26 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.34-1.52 (2H, m), 1.56-1.82 (2H, m), 1.83-2.03 (4H, m), 2.07-2.13 (6H, m), 2.37-2.46 (2H, m), 3.35-3.43 (3H, m), 3.60-3.85 (1H, m), 3.96-4.04 (3H, m), 4.09-4.21 (3H, m), 8.21-8.36 (1H, m), 8.39-8.51 (1H, m), 8.65-8.76 (2H, m), 8.98-9.04 (1H, m), 9.14-9.22 (2H, m), 9.26-9.33 (2H, m).

Example 798

25 N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide

30 A) tert-butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butylamido)cyclohexyl)carbamate

35 **[0442]** To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (1 g), DMAP (275 mg) and DMA (30 mL) was slowly added butyryl chloride (1.3 mL) at room temperature. The mixture was stirred at 70°C for 4 hr, and at 100°C for 2 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (214 mg). MS: [M+H]⁺ 471.3.

40 B) N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butylamide

[0443] A mixture of tert-butyl (trans-4-(1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butylamido)cyclohexyl)carbamate (214 mg) and TFA (2 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (144 mg).

45 C) N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide

50 **[0444]** A mixture of N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butylamide (144 mg), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (163 mg), DIPEA (0.2 mL) and DMF (2 mL) was stirred at 70°C for 3 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and NH, ethyl acetate/hexane) to give the title compound (66 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 0.73-0.82 (3H, m), 1.20-1.57 (6H, m), 1.79-2.02 (6H, m), 3.32-3.42 (3H, m), 3.66 (1H, br s), 3.98-4.07 (3H, m), 4.43 (1H, br s), 8.19-8.48 (2H, m), 8.68-8.78 (2H, m), 8.96-9.02 (1H, m), 9.15-9.22 (1H, m), 9.25-9.39 (3H, m).

Example 799

3-ethyl-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

A) tert-butyl (trans-4-(3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0445] A mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (300 mg) and 2 M ethylamine THF solution (2.6 mL) was stirred at 70°C for 2 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate/hexane to give the title compound (237 mg). MS: [M+H]⁺ 472.3.

B) 1-(trans-4-aminocyclohexyl)-3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0446] A mixture of tert-butyl (trans-4-(3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate (237 mg) and TFA (2 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (158 mg). MS: [M+H]⁺ 372.2.

C) 3-ethyl-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0447] To a solution of 1-(trans-4-aminocyclohexyl)-3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (44 mg) and 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (50 mg) in DMF (1.0 mL) was added DIPEA (0.04 mL) at room temperature. The reaction mixture was stirred at 70°C for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (29 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.00 (3H, q, J = 6.9 Hz), 1.34-1.73 (4H, m), 1.74-2.03 (4H, m), 2.98-3.14 (2H, m), 3.35-3.42 (3H, m), 3.55-3.82 (1H, m), 3.97-4.05 (3H, m), 4.16-4.36 (1H, m), 6.64-6.81 (1H, m), 8.25-8.39 (1H, m), 8.39-8.53 (2H, m), 8.68-8.77 (1H, m), 9.01 (1H, s), 9.09-9.22 (2H, m), 9.24-9.34 (2H, m).

Example 804

1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea A) tert-butyl (trans-4-(3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate

[0448] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (200 mg) and 1-amino-2-methylpropan-2-ol (46 mg) in THF (5.0 mL) was added DIPEA (0.23 mL) at room temperature, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (221 mg).

MS: [M+H]⁺ 516.3.

B) 1-(trans-4-aminocyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0449] A mixture of tert-butyl (trans-4-(3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)ureido)cyclohexyl)carbamate (221 mg) and TFA (3 mL) was stirred at room temperature for 1 hr. The solvent of the reaction mixture was evaporated under reduced pressure, and azeotropically distilled with toluene. The residue was purified by silica gel column chromatography (NH, ethyl acetate/methanol) to give the title compound (171 mg).

MS: [M+H]⁺ 416.3.

C) 1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea

[0450] To a solution of 1-(trans-4-aminocyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea (85 mg) and 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidine (70 mg) in DMF (1.0 mL) was added DIPEA (0.11 mL) at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (66 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (6H, s), 1.35-1.54 (2H, m), 1.59-2.05 (6H, m), 3.06 (2H, br d, J = 5.7 Hz), 3.59-3.82 (1H, m), 4.01 (3H, s), 4.22 (1H, s), 4.41-4.47 (1H, m), 6.60-6.74 (1H, m), 6.87 (1H, dd, J = 11.7, 2.6 Hz), 7.65-8.07 (1H, m), 8.07-8.21 (1H, m), 8.33-8.38 (1H, m), 8.58 (1H, d, J = 1.1 Hz), 8.65 (1H, d, J = 12.5 Hz), 9.17 (1H, d, J = 1.5 Hz), 9.30 (2H, s).

Example 820

2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

A) 2,2-difluoroethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0451] A mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (300 mg), DMAP (93 mg), DIPEA (268 mg) and 2,2-difluoroethanol (1.5 mL) was stirred at 70°C for 2 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (320 mg).

MS: [M+H-tBu+H]⁺ 425.2.

B) 2,2-difluoroethyl (trans-4-aminocyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0452] A mixture of 2,2-difluoroethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate (320 mg) and TFA (4.08 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH₃, ethyl acetate/hexane/methanol) to give the title compound (244 mg). MS: [M+H]⁺ 381.2.

C) 2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0453] A mixture of 2,2-difluoroethyl (trans-4-aminocyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate (30 mg), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (30 mg), DIPEA (0.69 mL) and acetonitrile (2 mL) was stirred at room temperature overnight. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol), and treated with ethyl acetate and hexane to give the title compound (23 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.31-1.72 (4H, m), 1.82-2.07 (4H, m), 3.34-3.41 (3H, m), 3.57-3.81 (1H, m), 3.86-3.98 (3H, m), 4.00-4.18 (1H, m), 4.24-4.45 (2H, m), 5.96-6.43 (1H, m), 8.04-8.16 (1H, m), 8.21-8.56 (4H, m), 8.67-8.78 (1H, m), 8.81-8.93 (1H, m), 8.97-9.05 (1H, m), 9.17-9.24 (1H, m).

Example 826

4,4-difluoro-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide

A) tert-butyl (trans-4-(4,4-difluoro-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butaneamido)cyclohexyl)carbamate

[0454] A mixture of 4,4-difluorobutanoic acid (1.35 g), oxalyl chloride (1.4 mL), DMF (0.01 mL) and diethyl ether (20 mL) was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give, 4,4-difluorobutanoyl chloride (1.43 g). A mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (400 mg), 4,4-difluorobutanoyl chloride (712 mg), DMAP (122 mg) and DMA (10 mL) was stirred at 70°C for 6 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (80 mg).

MS: [M+Na]⁺ 529.3.

B) 4,4-difluoro-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide

[0455] A mixture of tert-butyl (trans-4-(4,4-difluoro-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butaneamido)cyclohexyl)carbamate (80 mg) and TFA (1 mL) was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure. A mixture of the residue, 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (78 mg), DIPEA (0.08 mL) and DMF (1 mL) was stirred at 70°C for 4 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.21-1.57 (4H, m), 1.80-2.22 (8H, m), 3.33-3.40 (3H, m), 3.52-3.78 (1H, m), 4.02 (3H, d, J = 4.2 Hz), 4.42 (1H, br s), 5.81-6.26 (1H, m), 8.21-8.36 (1H, m), 8.36-8.48 (1H, m), 8.70 (1H, s), 8.73-8.82 (1H, m), 8.96-9.01 (1H, m), 9.16-9.22 (1H, m), 9.27-9.38 (3H, m).

Example 827

2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide

A) tert-butyl (trans-4-(2-ethoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamido)cyclohexyl)carbamate

[0456] To a mixture of 2-ethoxyacetic acid (1.82 mL), DMF (0.01 mL) and diethyl ether (20 mL) was slowly added oxalyl chloride (2.5 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give 2-ethoxyacetyl chloride (2.4 g). To a mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (600 mg), DMAP (183 mg) and DMA (15 mL) was added 2-ethoxyacetyl chloride (918 mg) at room temperature, and the mixture was stirred at 70°C overnight. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (99 mg).

MS: [M+Na]⁺ 509.3.

B) 2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide

[0457] A mixture of tert-butyl (trans-4-(2-ethoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamido)cyclohexyl)carbamate (99 mg), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (101 mg), DIPEA (0.11 mL) and DMF (1 mL) was stirred at 70°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (6 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.91 (3H, td, J = 7.0, 4.2 Hz), 1.32-1.55 (4H, m), 1.91 (4H, br d, J = 22.3 Hz), 3.22-3.29 (2H, m), 3.33-3.40 (3H, m), 3.62-3.77 (1H, m), 3.85-3.94 (2H, m), 3.99-4.05 (3H, m), 4.39 (1H, br s), 8.23-8.36 (1H, m),

8.37-8.48 (1H, m), 8.70 (1H, d, J = 2.3 Hz), 8.76 (1H, d, J = 12.1 Hz), 9.00 (1H, s), 9.17-9.22 (1H, m), 9.22-9.29 (1H, m), 9.30-9.37 (2H, m).

Example 831

2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamide

A) tert-butyl (trans-4-(2-ethoxy-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamido)cyclohexyl)carbamate

[0458] A mixture of 2-ethoxyacetic acid (0.30 mL), triphosgene (319 mg), DMF (0.01 mL) and THF (3 mL) was stirred at room temperature for 2 hr. The reaction mixture was concentrated to not more than half the volume under reduced pressure and added to a solution of tert-butyl (trans-4-((5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (300 mg) in pyridine (3 mL). The mixture was stirred at 60°C for 4 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (117 mg).
MS: [M+H]⁺ 459.3.

B) 2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamide

[0459] tert-Butyl (trans-4-(2-ethoxy-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamido)cyclohexyl)carbamate (50 mg) was dissolved in TFA (1 mL) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (2 mL), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (50 mg) and DIPEA (0.19 mL) were added at room temperature. The mixture was stirred at 60°C for 1 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol), and treated with ethyl acetate and hexane to give the title compound (43 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.87-0.98 (3H, m), 1.21-1.56 (4H, m), 1.76-2.06 (4H, m), 3.21-3.43 (5H, m), 3.53-3.77 (1H, m), 3.78-3.88 (2H, m), 3.88-3.97 (3H, m), 4.27-4.44 (1H, m), 8.06-8.17 (1H, m), 8.20-8.36 (1H, m), 8.36-8.49 (2H, m), 8.50-8.61 (1H, m), 8.66-8.74 (1H, m), 8.84-8.96 (1H, m), 8.96-9.03 (1H, m), 9.16-9.23 (1H, m).

Example 836

2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

A) 2-hydroxy-2-methylpropyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0460] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (100 mg), DIPEA (0.08 mL) and 2-methylpropane-1,2-diol (97 mg) in THF (2 mL) was added DMAP (26 mg) at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (91 mg).

MS: [M+H]⁺ 517.3.

B) 2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0461] A mixture of 2-hydroxy-2-methylpropyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (91 mg) and TFA (3.0 mL) was stirred at room temperature for 30 min. The solvent of

the reaction mixture was evaporated under reduced pressure, and the residue was azeotropically distilled with toluene. The residue was dissolved in DMF (1.0 mL), and 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (67 mg) and DIPEA (0.31 mL) were added at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol) to give the title compound (53 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.94-1.05 (6H, m), 1.33-1.53 (2H, m), 1.56-1.82 (2H, m), 1.84-2.08 (4H, m), 3.33-3.40 (3H, m), 3.57-3.79 (1H, m), 3.80-3.90 (2H, m), 3.98-4.04 (3H, m), 4.10-4.26 (1H, m), 4.49-4.61 (1H, m), 8.23-8.36 (1H, m), 8.37-8.50 (1H, m), 8.68-8.78 (2H, m), 8.98-9.07 (1H, m), 9.16-9.23 (2H, m), 9.25-9.35 (2H, m).

Example 838

2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

A) 2-hydroxy-2-methylpropyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0462] To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (150 mg), DIPEA (0.12 mL) and 2-methylpropane-1,2-diol (93 mg) in THF (2 mL) was added DMAP (42 mg) at room temperature. The reaction mixture was stirred at 70°C for 2 days. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (157 mg).

MS: [M+H]⁺ 489.3.

B) 2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate

[0463] A mixture of 2-hydroxy-2-methylpropyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate (82 mg) and TFA (3.0 mL) was stirred at room temperature for 30 min. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was azeotropically distilled with toluene. The residue was dissolved in DMF (1.0 mL), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (64 mg) and DIPEA (0.29 mL) were added at room temperature. The reaction mixture was stirred at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (42 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.89-1.03 (6H, m), 1.34-1.70 (4H, m), 1.81-2.02 (4H, m), 3.35-3.41 (3H, m), 3.56-3.77 (1H, m), 3.78-3.83 (2H, m), 3.89-3.96 (3H, m), 4.03-4.21 (1H, m), 4.45-4.58 (1H, m), 8.03-8.13 (1H, m), 8.21-8.35 (1H, m), 8.36-8.53 (3H, m), 8.72 (1H, d, J = 9.1 Hz), 8.81-8.91 (1H, m), 8.98-9.06 (1H, m), 9.11-9.29 (1H, m).

Example 841

2-hydroxy-2-methylpropyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate

[0464] 2-Hydroxy-2-methylpropyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate (91 mg) was dissolved in TFA (3.0 mL) at room temperature, and the mixture was stirred at room temperature for 30 min. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was azeotropically distilled with toluene. The residue was dissolved in DMF (1.0 mL), and 2-chloro-4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidine (100 mg) and DIPEA (0.31 mL) were added at room temperature. The reaction mixture was stirred at 70°C overnight. The reaction mixture was purified by HPLC (YMCTriartC18, mobile phase: water/acetonitrile (10 mM ammonium bicarbonate-based)) to give the title compound (17 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.01 (6H, s), 1.33-1.54 (2H, m), 1.55-1.78 (2H, m), 1.85 (4H, br d, J = 3.8 Hz), 3.56-3.77 (1H, m), 3.86 (2H, d, J = 3.0 Hz), 4.01 (3H, d, J = 2.3 Hz), 4.09-4.26 (1H, m), 4.56 (1H, d, J = 3.0 Hz), 7.98-8.20 (2H, m), 8.58-8.68 (1H, m),

8.71-8.76 (1H, m), 9.15-9.26 (1H, m), 9.31 (2H, d, J = 5.7 Hz), 13.35-13.66 (1H, m).

Example 848

5 2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

A) 2-(dimethylamino)ethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

10 **[0465]** To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (100 mg), DIPEA (0.08 mL), 2-(dimethylamino)ethan-1-ol (96 mg) and THF (3 mL) was added DMAP (26 mg) at room temperature. The mixture was stirred at 70°C overnight. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried
15 over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (61 mg).
MS: [M+H]⁺ 515.4.

20 B) 2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate

[0466] 2-(Dimethylamino)ethyl (trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate (60 mg) was dissolved in TFA (1 mL) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (2 mL), and 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (53 mg) and DIPEA (0.20 mL) were added at
25 room temperature. The mixture was stirred at 60°C for 1 hr. The reaction mixture was added to saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane/methanol), and treated with
30 ethyl acetate and diisopropyl ether to give the title compound (35 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.80 (4H, m), 1.81-2.04 (4H, m), 2.05-2.16 (6H, m), 2.34-2.46 (2H, m), 3.34-3.42 (3H, m), 3.54-3.83 (1H, m), 3.94-4.03 (3H, m), 4.03-4.19 (3H, m), 7.35-7.49 (1H, m), 8.13-8.36 (2H, m), 8.38-8.50 (1H, m), 8.67-8.77 (1H, m), 8.78-8.90 (1H, m), 8.98-9.08 (3H, m), 9.20 (1H, d, J = 1.9 Hz).

35 Example 849

1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea

40 **[0467]** To a mixture of tert-butyl (trans-4-((chlorocarbonyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (100 mg) and 1-amino-2-methylpropan-2-ol (23 mg) in THF (3.0 mL) was added DIPEA (0.075 mL) at room temperature, and the mixture was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate.
45 The solvent was evaporated under reduced pressure. The residue was dissolved in TFA (3.0 mL), and the mixture was stirred at room temperature for 30 min. The solvent of the reaction mixture was evaporated under reduced pressure, and the residue was azeotropically distilled with toluene. The residue was dissolved in DMF (1.0 mL), and 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-2-(methylsulfonyl)-5-(trifluoromethyl)pyrimidine (74 mg) and DIPEA (0.38 mL) were added at room temperature. The reaction mixture was stirred at 70°C for 3 hr. To the reaction mixture was added water at room
50 temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (51 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 1.02 (6H, s), 1.35-1.53 (2H, m), 1.55-1.75 (2H, m), 1.75-1.88 (2H, m), 1.88-2.05 (2H, m), 3.03 (2H, br d, J = 5.3 Hz), 3.60-3.78 (1H, m), 3.99 (3H, s), 4.15-4.34 (1H, m), 4.41-4.49 (1H, m), 6.08-6.24 (1H, m),
55 6.87 (1H, dd, J = 8.5, 2.5 Hz), 7.36 (1H, d, J = 8.3 Hz), 7.63-8.07 (1H, m), 8.06-8.18 (1H, m), 8.22 (1H, dd, J = 8.7, 2.6 Hz), 8.29-8.42 (1H, m), 8.65 (1H, d, J = 11.0 Hz), 8.88 (1H, d, J = 2.3 Hz), 8.98-9.10 (2H, m).

Example 858

N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxy-
ypirimidin-5-yl)pyridin-2-yl)butanamide

A) tert-butyl (trans-4-(N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)butylamido)cyclohexyl)carbamate

[0468] A mixture of tert-butyl (trans-4-((5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (1 g), DMAP (306 mg), butyryl chloride (1.25 mL) and DMA (15 mL) was stirred at 70°C overnight. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (400 mg).

MS: [M+H]⁺ 470.3.

B) N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)butylamide

[0469] A mixture of tert-butyl (trans-4-(N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)butylamido)cyclohexyl)carbamate (149 mg) and TFA (2 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (111 mg). MS: [M+H]⁺ 370.2.

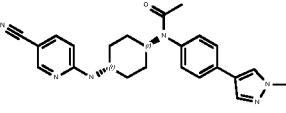
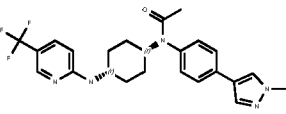
C) N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxy-
ypirimidin-5-yl)pyridin-2-yl)butanamide

[0470] A mixture of N-(trans-4-aminocyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)butylamide (111 mg), 2-(methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (172 mg), DIPEA (0.16 mL) and DMF (2 mL) was stirred at 70°C for 3 hr. 2-(Methylsulfonyl)-4-(5-(methylsulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidine (92 mg) and DIPEA (0.16 mL) were added, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was added to water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane and NH, ethyl acetate/hexane) to give the title compound (47.6 mg).

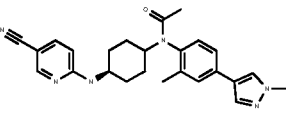
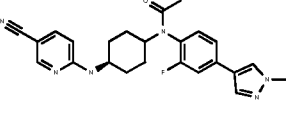
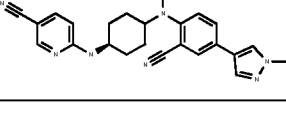
¹H NMR (300 MHz, DMSO-d₆) δ 0.70-0.81 (3H, m), 1.21-1.56 (6H, m), 1.78-2.02 (6H, m), 3.34-3.40 (3H, m), 3.63 (1H, br d, J = 2.6 Hz), 3.96-4.01 (3H, m), 4.41 (1H, br d, J = 3.4 Hz), 7.42-7.54 (1H, m), 8.21-8.36 (2H, m), 8.36-8.48 (1H, m), 8.70 (1H, d, J = 2.6 Hz), 8.89-9.02 (2H, m), 9.03-9.11 (2H, m), 9.16-9.23 (1H, m).

[0471] The Example compounds are shown in the following Tables. In the Tables, MS shows the measured values. The compounds of Examples 1 - 19, 21 - 187, 191 - 198, 200 - 318, 320 - 439, 441 - 468, 470 - 481, 486 - 494, 496 - 526, 528, 529, 531, 533 - 535, 537, 540, 541, 543 - 551, 554 - 565, 567 - 573, 576, 578 - 580, 583 - 586, 590, 591, 593, 594, 597, 598, 601, 602, 604, 607, 613, 615, 616, 621, 622, 624, 632, 634 - 692, 694 - 728, 730 - 739, 741, 745 - 763, 765, 768 - 797, 800 - 803, 805 - 819, 821 - 825, 828 - 830, 832 - 835, 837, 839, 840, 842 - 847, 850 - 857 and Reference Examples 1 - 10 in the following Tables were produced according to the methods shown in the above-mentioned Examples or a method analogous thereto.

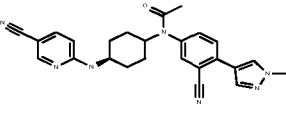
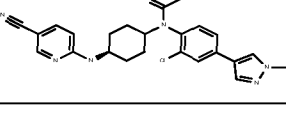
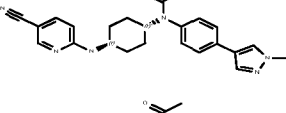
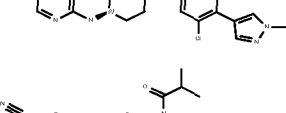
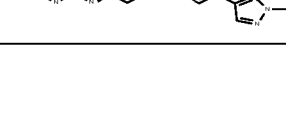
[Table 1-1]

Ex. No.	IUPAC name	structural formula	salt	MS
1	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			413.1
2	N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)acetamide			458.2

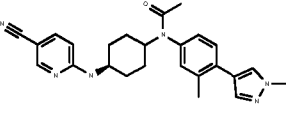
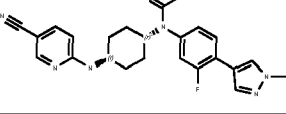
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
3	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(2-methyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			429.3
4	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			433.1
5	N-(2-cyano-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)acetamide			440.2

[Table 1-2]

Ex. No.	IUPAC name	structural formula	salt	MS
6	N-(3-cyano-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)acetamide			440.2
7	N-(2-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)acetamide			449.1
8	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanamide			429.2
9	N-(3-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)acetamide			449.1
10	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-2-methyl-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanamide			443.3

[Table 1-3]

Ex. No.	IUPAC name	structural formula	salt	MS
11	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(3-methyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			429.2
12	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			433.1

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
13	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)benzamide			477.3
14	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			445.2
15	benzyl (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl) (4-(1-methyl-1H-pyrazol-4-yl)phenyl)carbamate			507.3

[Table 1-4]

Ex. No.	IUPAC name	structural formula	salt	MS
16	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)tetrahydro-2H-pyran-4-carboxamide			485.3
17	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			506.2
18	methyl (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl) (4-(1-methyl-1H-pyrazol-4-yl)phenyl)carbamate			431.1
19	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-ethyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			444.3
21	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(3-furyl)phenyl)urea			492.3

[Table 1-5]

Ex. No.	IUPAC name	structural formula	salt	MS
22	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-(trifluoromethyl)phenyl)acetamide			483.2
23	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			445.2
24	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanamide			447.1
25	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanamide			457.1
26	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(2,6-dichloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			483.1

[Table 1-6]

Ex. No.	IUPAC name	structural formula	salt	MS
27	N-(3-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)propanamide			461.2
28	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(cyclohexylmethyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl) urea			512.2
29	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(3-methoxybenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl) urea			536.3
30	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(4-methoxybenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl) urea			536.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
31	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(4-fluorobenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			524.3

[Table 1-7]

Ex. No.	IUPAC name	structural formula	salt	MS
32	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(3-fluorobenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			524.3
33	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(2-methoxybenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			536.3
34	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(pyridin-2-ylmethyl)urea			507.3
35	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(2-fluorobenzyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			524.3
36	3-benzyl-1-(4-bromo-phenyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			504.1

[Table 1-8]

Ex. No.	IUPAC name	structural formula	salt	MS
37	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-phenoxyacetamide			507.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
38	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)urea			507.3
39	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(pyridin-3-ylmethyl)urea			507.3
40	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(2-furylmethyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			496.2
41	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(pyridin-4-ylmethyl)urea			507.3

[Table 1-9]

Ex. No.	IUPAC name	structural formula	salt	MS
42	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-phenylacetamide			491.3
43	2-(4-bromophenyl)-N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)acetamide			569.2
44	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(3,5-dimethyl-1,2-oxazol-4-yl)phenyl)urea			521.2
45	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-cyanopyrimidin-5-yl)phenyl)urea			529.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
46	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-furyl)phenyl)urea			492.3

[Table 1-10]

Ex. No.	IUPAC name	structural formula	salt	MS
47	1-(4-(6-aminopyridin-3-yl)phenyl)-3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			518.3
48	1-(4-(2-aminopyridin-3-yl)phenyl)-3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			518.3
49	1-(4-(2-aminopyridin-4-yl)phenyl)-3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			518.3
50	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(morpholin-4-ylmethyl)phenyl)urea			525.4
51	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-methylphenyl)urea			440.2

[Table 1-11]

Ex. No.	IUPAC name	structural formula	salt	MS
52	3-benzyl-1-biphenyl-4-yl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			502.3
53	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(3'-methoxybiphenyl-4-yl)urea			532.2

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
54	3-benzyl-1-(2'-cyanobiphenyl-4-yl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			527.2
55	3-benzyl-1-(4'-cyanobiphenyl-4-yl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			527.2
56	3-benzyl-1-(3'-cyanobiphenyl-4-yl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			527.3

[Table 1-12]

Ex. No.	IUPAC name	structural formula	salt	MS
57	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(2-methoxyethyl)phenyl)urea			484.3
58	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(piperidin-1-ylmethyl)phenyl)urea			523.4
59	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			533.3
60	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(6-methoxypyridin-2-yl)phenyl)urea			533.3
61	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(4-(6-methoxypyridin-3-yl)phenyl)urea			533.3

[Table 1-13]

Ex. No.	IUPAC name	structural formula	salt	MS
62	2-(4-(4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1H-pyrazol-1-yl)acetamide			549.3
63	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)phenyl)urea			564.3
64	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-(2-(morpholin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)urea			605.4
65	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-ethyl-1H-pyrazol-4-yl)phenyl)urea			520.3
66	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-isopropyl-1H-pyrazol-4-yl)phenyl)urea			534.3

[Table 1-14]

Ex. No.	IUPAC name	structural formula	salt	MS
67	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-methoxypyridin-3-yl)phenyl)urea			533.3
68	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(methoxymethyl)phenyl)urea			470.3
69	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(3,6-dihydro-2H-pyran-4-yl)phenyl)urea			508.3
70	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)urea			521.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
71	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-vinylphenyl)urea			452.2

[Table 1-15]

Ex. No.	IUPAC name	structural formula	salt	MS
72	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(prop-1-en-2-yl)phenyl)urea			466.2
73	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-(pyridin-2-ylmethyl)-1H-pyrazol-4-yl)phenyl)urea			583.3
74	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)phenyl)urea			583.3
75	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)phenyl)urea			546.3
76	3-(4-(4-((benzylcarbamoyl) (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1H-pyrazol-1-yl)propanamide			563.3

[Table 1-16]

Ex. No.	IUPAC name	structural formula	salt	MS
77	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-thienyl)phenyl)urea			508.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
78	3-benzyl-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			550.2
79	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-3-yl)phenyl)urea			503.3
80	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(morpholin-4-yl)phenyl)urea			511.2
81	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyrimidin-5-yl)phenyl)urea			504.2

[Table 1-17]

Ex. No.	IUPAC name	structural formula	salt	MS
82	1-(4-(4-acetylpiperazin-1-yl)phenyl)-3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			552.4
83	1-(4-anilinophenyl)-3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			517.2
84	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-3-yl)phenyl)urea			506.2
85	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1H-pyrazol-4-yl)phenyl)urea			492.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
86	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-4-yl)phenyl)urea			503.2

[Table 1-18]

Ex. No.	IUPAC name	structural formula	salt	MS
87	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)urea			506.3
88	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-2-yl)phenyl)urea			503.2
89	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-phenylurea			426.2
90	1-benzyl-3-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-methyl-3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			520.3
91	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-((1R)-1-phenylethyl) urea			520.3

[Table 1-19]

Ex. No.	IUPAC name	structural formula	salt	MS
92	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-((1S)-1-phenylethyl)urea			520.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
93	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-((2-methoxypyridin-4-yl)-methyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			537.2
94	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(3-(methylsulfonyl)benzyl)urea			584.2
95	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			508.4
96	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			507.3

[Table 1-20]

Ex. No.	IUPAC name	structural formula	salt	MS
97	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(4-methoxypiperidin-1-yl)phenyl)urea			539.3
98	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((2-methoxyethyl)amino)-phenyl)urea			499.3
99	3-benzyl-1-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			534.3
100	1-(4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)-phenyl)piperidine-4-carboxamide			552.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
101	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(4-(dimethylamino)piperidin-1-yl)phenyl) urea			552.4

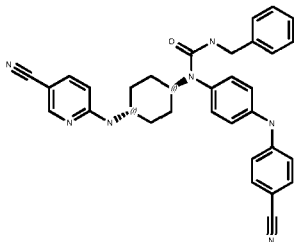
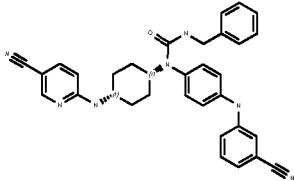
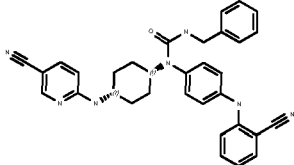
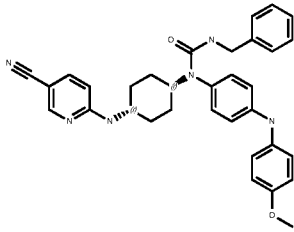
[Table 1-21]

Ex. No.	IUPAC name	structural formula	salt	MS
102	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(2-oxa-7-azaspiro[3.5]nonan-7-yl) phenyl)urea			551.3
103	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(2-oxa-6-azaspiro[3.5]nonan-6-yl) phenyl)urea			551.4
104	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(1,1-dioxide-thiomorpholin-4-yl)phenyl) urea			559.3
105	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(4-methylpiperazin-1-yl)phenyl)urea			524.3
106	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl) urea			588.3

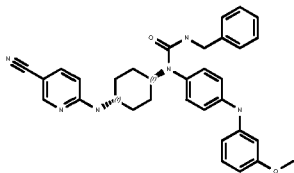
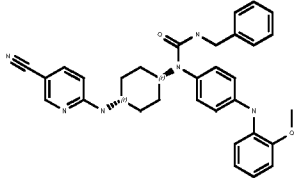
[Table 1-22]

Ex. No.	IUPAC name	structural formula	salt	MS
107	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino) cyclohexyl)-1-(4-((3S)-3-methoxypyrrolidin-1-yl)phenyl) urea			525.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
108	3-benzyl-1-(4-((4-cyanophenyl)amino)phenyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			542.3
109	3-benzyl-1-(4-((3-cyanophenyl)amino)phenyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			542.3
110	3-benzyl-1-(4-((2-cyanophenyl)amino)phenyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			542.3
111	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((4-methoxyphenyl)amino)phenyl)urea			547.3

[Table 1-23]

Ex. No.	IUPAC name	structural formula	salt	MS
112	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((3-methoxyphenyl)amino)phenyl)urea			547.3
113	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((2-methoxyphenyl)amino)phenyl)urea			547.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
114	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((1-methyl-1H-pyrazol-5-yl)amino)phenyl)urea			521.3
115	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((1-methyl-1H-pyrazol-4-yl)amino)phenyl)urea			521.3
116	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((1-methyl-1H-pyrazol-3-yl)amino)phenyl)urea			521.3

[Table 1-24]

Ex. No.	IUPAC name	structural formula	salt	MS
117	4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)-N,N-dimethylbenzamido			497.3
118	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			508.3
119	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-oxopyrrolidin-1-yl)phenyl)urea			509.3
120	4'-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)biphenyl-3-carboxamide			545.3

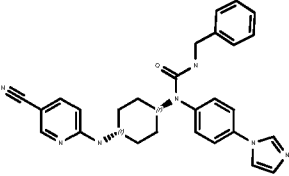
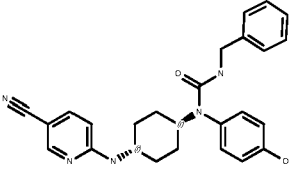
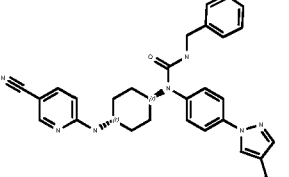
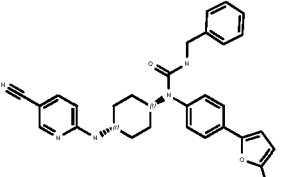
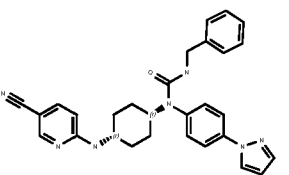
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
121	4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)benzoic acid			470.2

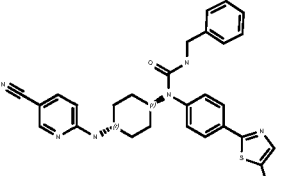
[Table 1-25]

Ex. No.	IUPAC name	structural formula	salt	MS
122	4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)benzamide			469.3
123	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyrazin-2-yl)phenyl)urea			504.2
124	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1H-pyrazol-1-yl)phenyl)urea			492.3
125	ethyl 1-(4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1H-pyrazole-4-carboxylate			564.3
126	methyl 5-(4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-2-furoate			550.2

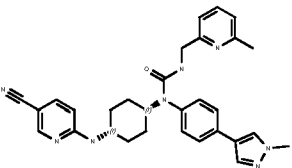
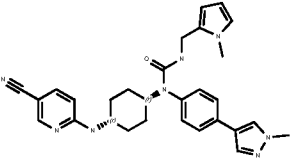
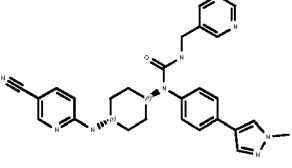
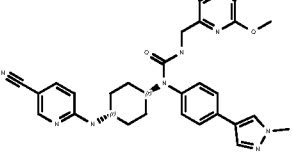
[Table 1-26]

Ex. No.	IUPAC name	structural formula	salt	MS
127	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1H-imidazol-1-yl)phenyl)urea			492.3
128	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-hydroxyphenyl)urea			442.2
129	1-(4-((benzylcarbamoyl) (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1H-pyrazole-4-carboxylic acid			536.3
130	5-(4-((benzylcarbamoyl) (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-2-furamide			535.2
131	1-(4-((benzylcarbamoyl) (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1H-pyrazole-4-carboxamide			535.3

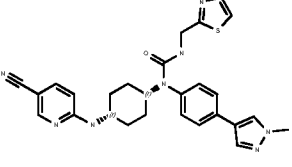
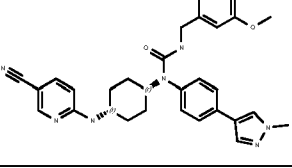
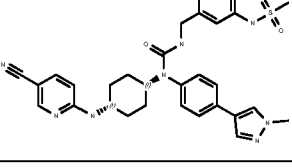
[Table 1-27]

Ex. No.	IUPAC name	structural formula	salt	MS
132	2-(4-((benzylcarbamoyl) (trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1,3-thiazole-5-carboxamide			552.2

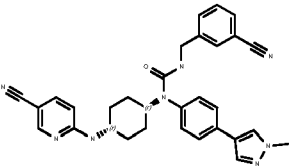
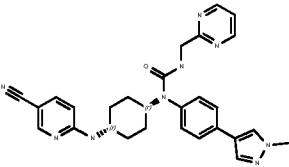
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
133	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-((6-methylpyridin-2-yl)methyl)urea			521.3
134	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-((1-methyl-1H-pyrrol-2-yl)methyl)urea			509.3
135	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(pyrimidin-5-ylmethyl)urea			508.3
136	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-((6-methoxypyridin-2-yl)methyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			537.3

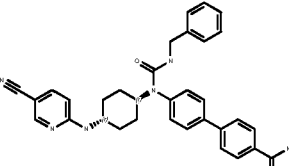
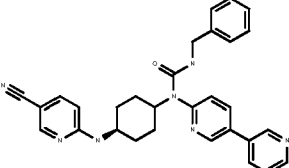
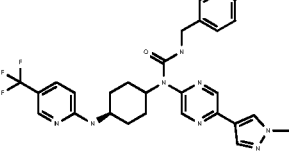
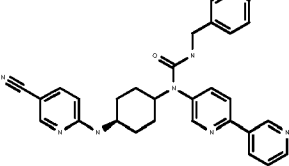
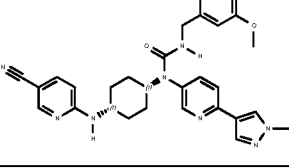
[Table 1-28]

Ex. No.	IUPAC name	structural formula	salt	MS
137	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(1,3-thiazol-2-ylmethyl)urea			513.2
138	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-((5-methoxypyridin-3-yl)methyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			537.3
139	N-(3-(((trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)(4-(1-methyl-1H-pyrazol-4-yl)phenyl)carbamoyl)amino)methyl)phenyl)-methanesulfonamide			599.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
140	3-(3-cyanobenzyl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			531.3
141	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(pyrimidin-2-ylmethyl)urea			508.3

[Table 1-29]

Ex. No.	IUPAC name	structural formula	salt	MS
142	4'-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)biphenyl-4-carboxamide			545.3
143	3-benzyl-1-(3,3'-bipyridin-6-yl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			504.2
144	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			551.3
145	3-benzyl-1-(2,3'-bipyridin-5-yl)-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)urea			504.2
146	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(3-methoxybenzyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)urea			537.2

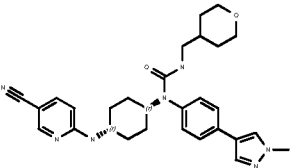
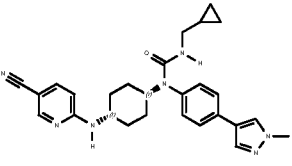
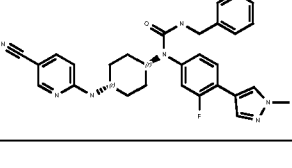
[Table 1-30]

Ex. No.	IUPAC name	structural formula	salt	MS
147	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-3-yl)phenyl)urea hydrochloride		HCl	503.3
148	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			550.3
149	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(6'-oxo-1',6'-dihydro-2,3'-bipyridin-5-yl)urea			520.2
150	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(6'-oxo-1',6'-dihydro-3,3'-bipyridin-6-yl)urea			520.2
151	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(6-oxo-1,6-dihydropyridin-3-yl)-pyridazin-3-yl)urea			521.3

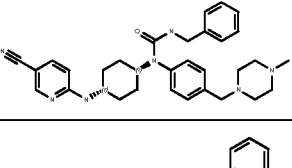
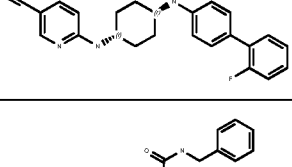
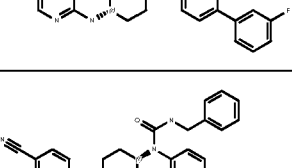
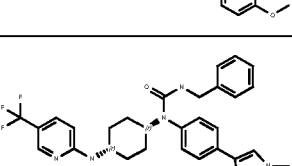
[Table 1-31]

Ex. No.	IUPAC name	structural formula	salt	MS
152	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea			508.4
153	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(2,2-dimethylpropyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			486.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
154	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(tetrahydro-2H-pyran-4-ylmethyl)urea			514.3
155	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-3-(cyclopropylmethyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			470.3
156	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			524.3

[Table 1-32]

Ex. No.	IUPAC name	structural formula	salt	MS
157	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)urea			538.4
158	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(2'-fluorobiphenyl-4-yl)urea			520.3
159	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(3'-fluorobiphenyl-4-yl)urea			520.2
160	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4'-methoxybiphenyl-4-yl)urea			532.2
161	3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			549.3

[Table 1-33]

Ex. No.	IUPAC name	structural formula	salt	MS
162	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-2-ylamino)phenyl)urea			518.3
163	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-3-ylamino)phenyl)urea			518.3
164	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-4-ylamino)phenyl)urea			518.3
165	2-(4-((benzylcarbamoyl)(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)amino)phenyl)-1,3-thiazole-4-carboxamide			552.3
166	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(6-oxo-1,6-dihydropyridin-2-yl)phenyl)urea			519.2

[Table 1-34]

Ex. No.	IUPAC name	structural formula	salt	MS
167	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			519.3
168	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea			519.2

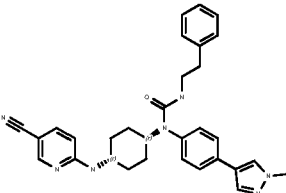
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
169	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-oxo-1,2-dihydropyridin-3-yl)phenyl)urea			519.2
170	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(5-(pyridin-3-yl)-pyrazin-2-yl)urea			505.3
171	3-benzyl-1-(trans-4-((5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			507.3

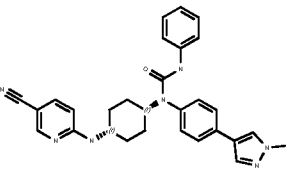
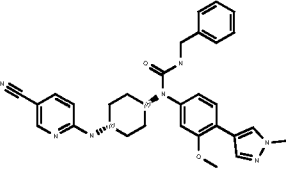
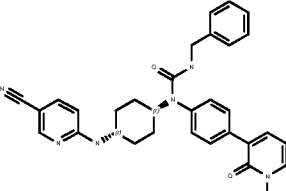
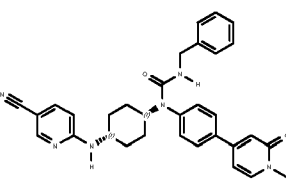
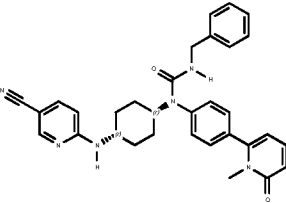
[Table 1-35]

Ex. No.	IUPAC name	structural formula	salt	MS
172	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			551.3
173	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(pyridin-3-yl)phenyl)urea methanesulfonate		MsOH	503.3
174	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(2-thienylmethyl)urea			512.3
175	N-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-phenylpropaneamide			505.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
176	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-(2-phenylethyl)urea			520.2

[Table 1-36]

Ex. No.	IUPAC name	structural formula	salt	MS
177	1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-3-phenylurea			492.3
178	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			536.3
179	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl)urea			533.3
180	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl) urea			533.3
181	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)phenyl)urea			533.3

[Table 1-37]

Ex. No.	IUPAC name	structural formula	salt	MS
182	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(1'-methyl-6'-oxo-1',6'-dihydro-2,3'-bipyridin-5-yl)urea			534.3
183	3-benzyl-1-phenyl-1-(trans-4-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			469.2
184	3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1-(trans-4-(pyridin-2-ylamino)cyclohexyl) urea			481.3
185	3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1-(trans-4-(pyrimidin-2-ylamino)cyclohexyl)urea			482.3
186	2-((trans-4-((benzylcarbamoyl) (4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)amino)p yrimidine-5-carboxamide			525.3

[Table 1-38]

Ex. No.	IUPAC name	structural formula	salt	MS
187	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(4-(2-oxopyridine-1(2H)-yl)phenyl)urea			519.3
191	3-benzyl-1-(trans-4-((5-fluoropyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			500.3
192	3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1-(trans-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) urea			550.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
193	3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1-(trans-4-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)urea			559.4
194	3-benzyl-1-(trans-4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			548.3

[Table 1-39]

Ex. No.	IUPAC name	structural formula	salt	MS
195	3-benzyl-1-(trans-4-((4-(difluoromethoxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			548.3
196	3-benzyl-1-(trans-4-((4-(4-methoxy-1H-pyrazol-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			578.3
197	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			571.3
198	N-(2-((trans-4-((benzylcarbamoyl)(4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)cyclohexyl)amino)pyrimidin-4-yl)-cyclopropanecarboxamide			565.4
199	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			580.4

[Table 1-40]

Ex. No.	IUPAC name	structural formula	salt	MS
200	3-benzyl-1-(trans-4-((5-cyano-4-((2-oxo-2,3-dihydro-1H-indol-5-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			651.3
201	3-benzyl-1-(trans-4-((5-cyano-4-(1H-imidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea hydrochloride		HCl	573.5
202	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-imidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			587.4
203	3-benzyl-1-(trans-4-((5-chloro-4-(morpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			601.4
204	3-benzyl-1-(trans-4-((5-chloro-4-(2-(methylsulfonyl)phenoxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			686.4

[Table 1-41]

Ex. No.	IUPAC name	structural formula	salt	MS
205	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-benzimidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			637.6
206	3-benzyl-1-(trans-4-((5-chloro-4-((2-(methylsulfonyl)phenyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			685.4
207	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
208	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			574.5
209	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			574.5

[Table 1-42]

Ex. No.	IUPAC name	structural formula	salt	MS
210	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			588.5
211	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			588.5
212	N ³ -(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)-beta-alanineamide			594.4
213	3-benzyl-1-(trans-4-((5-cyano-4-((2,3-dihydroxypropyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			597.4
214	3-benzyl-1-(trans-4-((5-cyano-4-((2-cyanoethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			574.3

[Table 1-43]

Ex. No.	IUPAC name	structural formula	salt	MS
215	3-benzyl-1-(trans-4-((5-cyano-4-((2,2-difluoro-3-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			617.4
216	3-benzyl-1-(trans-4-((5-cyano-4-(2-(hydroxymethyl)piperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
217	3-benzyl-1-(trans-4-((5-cyano-4-(3-oxo-2,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5
218	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxo-1-oxa-3,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			662.5
219	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxo-2,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5

[Table 1-44]

Ex. No.	IUPAC name	structural formula	salt	MS
220	3-benzyl-1-(trans-4-((5-cyano-4-(1,3-dioxo-2,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			674.5
221	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxo-1,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
222	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxo-1,7-diazaspiro [3.5]nona-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
223	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxo-1,7-diazaspiro [4.4]nona-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
224	3-benzyl-1-(trans-4-((5-cyano-4-((1H-imidazol-2-ylmethyl) amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			603.5

[Table 1-45]

Ex. No.	IUPAC name	structural formula	salt	MS
225	3-benzyl-1-(trans-4-((5-cyano-4-(((1-methyl-1H-imidazol-2-yl)methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			617.4
226	3-benzyl-1-(trans-4-((4-(benzylamino)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			613.5
227	3-benzyl-1-(trans-4-((5-cyano-4-((pyridin-2-ylmethyl) amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			614.5
228	3-benzyl-1-(trans-4-((5-cyano-4-((pyridin-3-ylmethyl) amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			614.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
229	3-benzyl-1-(trans-4-((5-cyano-4-((pyridin-4-ylmethyl) amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			614.5

[Table 1-46]

Ex. No.	IUPAC name	structural formula	salt	MS
230	N-(3-(((2-((trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide			719.4
231	3-benzyl-1-(trans-4-((5-cyano-4-((pyrazin-2-ylmethyl) amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
232	3-benzyl-1-(trans-4-((5-cyano-4-(((5-oxopyrrolidin-2-yl) methyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.5
233	3-benzyl-1-(trans-4-((5-cyano-4-((tetrahydrofuran-2-ylmethyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.5
234	3-benzyl-1-(trans-4-((5-cyano-4-((tetrahydrofuran-3-ylmethyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.5

[Table 1-47]

Ex. No.	IUPAC name	structural formula	salt	MS
235	3-benzyl-1-(trans-4-((5-cyano-4-((1-methylpyrrolidin-2-yl)methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.6
236	3-benzyl-1-(trans-4-((5-cyano-4-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			634.5
237	3-benzyl-1-(trans-4-((5-cyano-4-(tetrahydrofuran-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
238	3-benzyl-1-(trans-4-((5-cyano-4-((3,3,3-trifluoro-2-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			635.5
239	3-benzyl-1-(trans-4-((5-cyano-4-((1-hydroxypropan-2-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			581.4

[Table 1-48]

Ex. No.	IUPAC name	structural formula	salt	MS
240	3-benzyl-1-(trans-4-((5-cyano-4-((1-(hydroxymethyl)cyclopropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
241	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxycyclohexyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
242	3-benzyl-1-(trans-4-((5-cyano-4-((2-furylmethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			603.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
243	3-benzyl-1-(trans-4-((5-cyano-4-((2-(dimethylamino)ethyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			594.4
244	3-benzyl-1-(trans-4-((5-cyano-4-((2-(morpholin-4-yl)ethyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			636.6

[Table 1-49]

Ex. No.	IUPAC name	structural formula	salt	MS
245	3-benzyl-1-(trans-4-((5-cyano-4-((pyrimidin-2-ylmethyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
246	3-benzyl-1-(trans-4-((5-cyano-4-((pyridazin-3-ylmethyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
247	3-benzyl-1-(trans-4-((5-cyano-4-((pyrimidin-4-ylmethyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
248	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxy-4-(trifluoromethyl)-piperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			675.4
249	3-benzyl-1-(trans-4-((5-cyano-4-(4-fluoro-4-(hydroxymethyl)-piperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			639.5

[Table 1-50]

Ex. No.	IUPAC name	structural formula	salt	MS
250	3-benzyl-1-(trans-4-((5-cyano-4-((2-(trifluoromethoxy)ethyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			635.5
251	3-benzyl-1-(trans-4-((5-cyano-4-(3-(methylsulfonyl)azetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			641.4
252	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxa-6-azaspiro[3.5]nona-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
253	3-benzyl-1-(trans-4-((5-cyano-4-(4,4-difluoropiperidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			627.4
254	3-benzyl-1-(trans-4-((5-cyano-4-(5,6-dihydro[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			630.4

[Table 1-51]

Ex. No.	IUPAC name	structural formula	salt	MS
255	3-benzyl-1-(trans-4-((5-cyano-4-(2,2-difluoromorpholin-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			629.4
256	3-benzyl-1-(trans-4-((5-cyano-4-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.4
257	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxypropyl)(methyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
258	3-benzyl-1-(trans-4-((5-cyano-4-(6,6-difluoro-3-azabicyclo-[3.1.0]hexa-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			625.5
259	3-benzyl-1-(trans-4-((5-cyano-4-(((5-cyclopropyl-1,3,4-oxadiazol-2-yl)methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			645.5

[Table 1-52]

Ex. No.	IUPAC name	structural formula	salt	MS
260	3-benzyl-1-(trans-4-((4-(((3-tert-butyl-1H-pyrazol-5-yl)methyl)amino)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			659.5
261	3-benzyl-1-(trans-4-((5-cyano-4-((3-(methylsulfonyl)benzyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			691.4
262	3-benzyl-1-(trans-4-((5-cyano-4-((3-(methylsulfonyl)propyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			643.4
263	3-benzyl-1-(trans-4-((4-(butylamino)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			579.5
264	3-benzyl-1-(trans-4-((5-cyano-4-((pyrrolidin-3-yl)methyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-yl) urea trifluoroacetate		CF ₃ CO OH	606.5

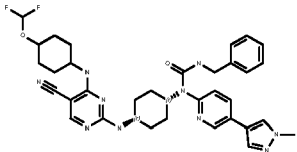
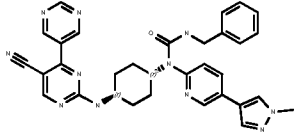
[Table 1-53]

Ex. No.	IUPAC name	structural formula	salt	MS
265	3-benzyl-1-(trans-4-((5-cyano-4-(pyrrolidin-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea trifluoroacetate		CF ₃ COOH	592.5
266	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-8-azabicyclo[3.2.1]octa-8-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
267	3-benzyl-1-(trans-4-((5-cyano-4-(9-oxa-2-azaspiro[5.5]undeca-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			661.6
268	3-benzyl-1-(trans-4-((5-cyano-4-(8-oxa-2-azaspiro[4.5]deca-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.6
269	3-benzyl-1-(trans-4-((5-cyano-4-(3-oxo-2,7-diazaspiro[4.5]deca-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5

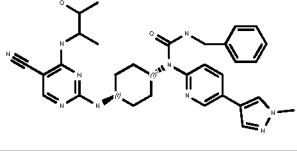
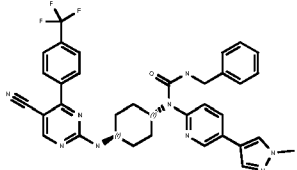
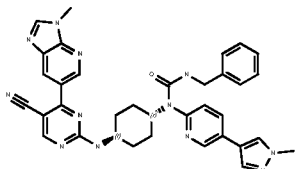
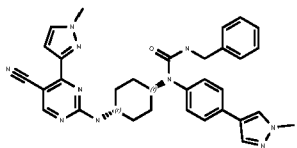
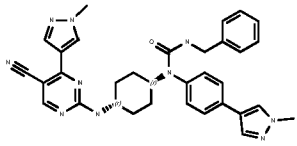
[Table 1-54]

Ex. No.	IUPAC name	structural formula	salt	MS
270	3-benzyl-1-(trans-4-((5-cyano-4-((dicyclopropylmethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			617.4
271	3-benzyl-1-(trans-4-((5-cyano-4-(3-(difluoromethyl)azetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			613.4
272	3-benzyl-1-(trans-4-((5-cyano-4-(3-(difluoromethoxy)pyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			643.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
273	3-benzyl-1-(trans-4-((5-cyano-4-((4-(difluoromethoxy)cyclohexyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			671.5
274	3-benzyl-1-(trans-4-((5-cyano-4,5'-bipyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			586.3

[Table 1-55]

Ex. No.	IUPAC name	structural formula	salt	MS
275	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxybutan-2-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4
276	3-benzyl-1-(trans-4-((5-cyano-4-(4-(trifluoromethyl)phenyl)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			652.5
277	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			639.4
278	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			587.4
279	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			587.4

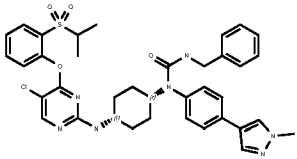
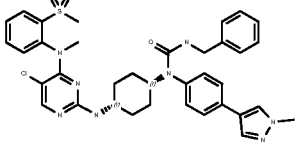
[Table 1-56]

Ex. No.	IUPAC name	structural formula	salt	MS
280	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			573.4
281	3-benzyl-1-(trans-4-((5-cyano-4-((3-methoxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			594.4
282	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxyethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			566.4
283	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxypropyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			581.5
284	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			573.5

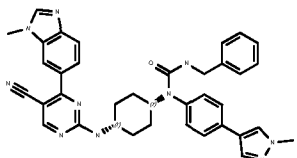
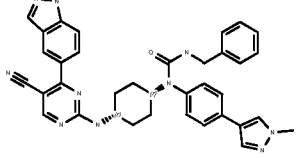
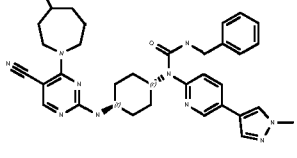
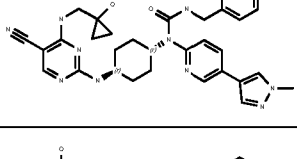
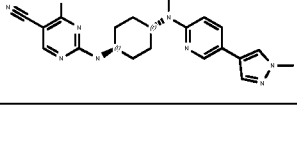
[Table 1-57]

Ex. No.	IUPAC name	structural formula	salt	MS
285	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea formate		formic acid	585.2
286	3-benzyl-1-(trans-4-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			559.4
287	3-benzyl-1-(trans-4-((5-chloro-4-(1,1-dioxidethiomorpholin-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			649.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
288	3-benzyl-1-(trans-4-((5-chloro-4-(2-(isopropylsulfonyl)phenoxy)-pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			714.4
289	3-benzyl-1-(trans-4-((5-chloro-4-(methyl (2-(methylsulfonyl)-phenyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			699.5

[Table 1-58]

Ex. No.	IUPAC name	structural formula	salt	MS
290	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-benzimidazol-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			637.5
291	3-benzyl-1-(trans-4-((5-cyano-4-(1H-indazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			623.5
292	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
293	3-benzyl-1-(trans-4-((5-cyano-4-(((1-hydroxycyclopropyl)methyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
294	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxyazetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			579.4

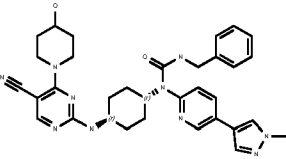
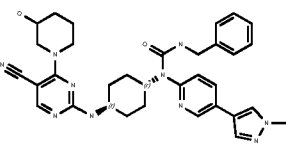
[Table 1-59]

Ex. No.	IUPAC name	structural formula	salt	MS
295	3-benzyl-1-(trans-4-((5-cyano-4-(3-cyano-3-methylpyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			616.4
296	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxypyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
297	3-benzyl-1-(trans-4-((5-cyano-4-(3-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.5
298	3-benzyl-1-(trans-4-((5-cyano-4-(2-(2-hydroxyethyl)pyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
299	3-benzyl-1-(trans-4-((5-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.4

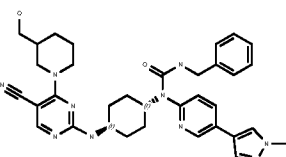
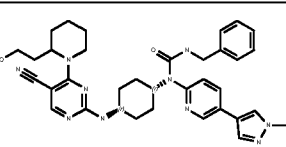
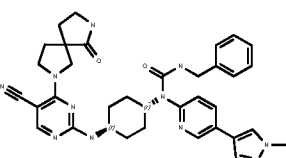
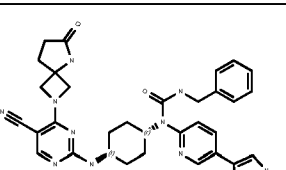
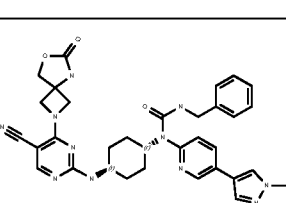
[Table 1-60]

Ex. No.	IUPAC name	structural formula	salt	MS
300	3-benzyl-1-(trans-4-((5-cyano-4-(3-oxopiperazin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			606.5
301	3-benzyl-1-(trans-4-((5-cyano-4-(1,1-dioxidethiomorpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			641.4
302	1-(trans-4-((4-(4-acetylpiperazin-1-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			634.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
303	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxypiperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.4
304	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxypiperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.4

[Table 1-61]

Ex. No.	IUPAC name	structural formula	salt	MS
305	3-benzyl-1-(trans-4-((5-cyano-4-(3-(hydroxymethyl)piperidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
306	3-benzyl-1-(trans-4-((5-cyano-4-(2-(2-hydroxyethyl)piperidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			635.5
307	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxo-2,7-diazaspiro[4.4]nona-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
308	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxo-2,5-diazaspiro[3.4]octa-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.5
309	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxo-7-oxa-2,5-diazaspiro-[3.4]octa-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			634.5

[Table 1-62]

Ex. No.	IUPAC name	structural formula	salt	MS
310	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-7-azaspiro[3.5]nona-7-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
311	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxa-7-azaspiro[3.5]nona-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
312	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-8-azaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.5
313	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxa-8-azaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.5
314	3-benzyl-1-(trans-4-((5-cyano-4-(3-fluoro-1-oxa-8-azaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			665.5

[Table 1-63]

Ex. No.	IUPAC name	structural formula	salt	MS
315	3-benzyl-1-(trans-4-((5-cyano-4-(3,3-difluoro-1-oxa-8-azaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			683.5
316	3-benzyl-1-(trans-4-((5-cyano-4-(5,6-dihydroimidazo[1,5-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			629.4

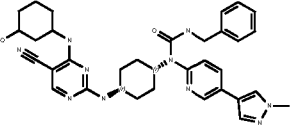
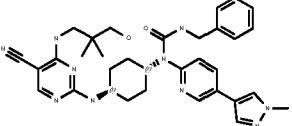
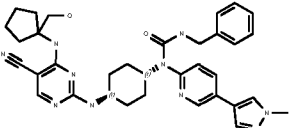
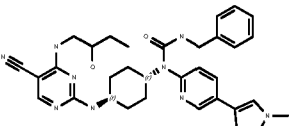
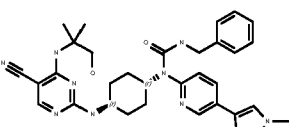
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Ex. No.	IUPAC name	structural formula	salt	MS
317	3-benzyl-1-(trans-4-((5-cyano-4-(5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			629.5
318	3-benzyl-1-(trans-4-((5-cyano-4-((1-methylpyrrolidin-3-yl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			606.5
319	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			579.4

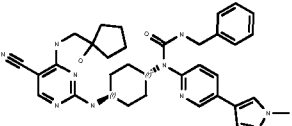
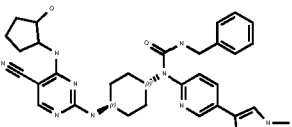
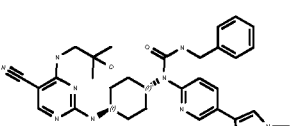
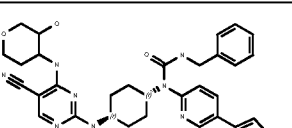
[Table 1-64]

Ex. No.	IUPAC name	structural formula	salt	MS
320	3-benzyl-1-(trans-4-((5-cyano-4-((1,1-dioxide-thietan-3-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			625.2
321	3-benzyl-1-(trans-4-((4-((5-tert-butyl-1,3-oxazol-2-yl)methoxy)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			661.5
322	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			574.3
323	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			589.5
324	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxybutyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4

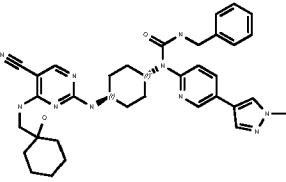
[Table 1-65]

Ex. No.	IUPAC name	structural formula	salt	MS
325	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxycyclohexyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
326	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxy-2,2-dimethylpropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.5
327	3-benzyl-1-(trans-4-((5-cyano-4-((1-(hydroxymethyl)cyclopentyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
328	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxybutyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4
329	3-benzyl-1-(trans-4-((5-cyano-4-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4

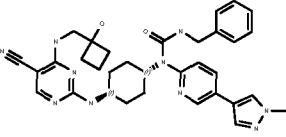
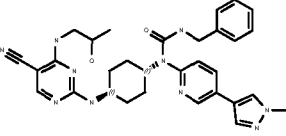
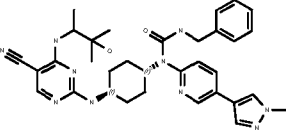
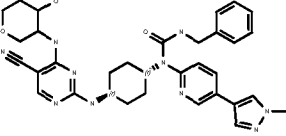
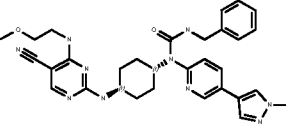
[Table 1-66]

Ex. No.	IUPAC name	structural formula	salt	MS
330	3-benzyl-1-(trans-4-((5-cyano-4-(((1-hydroxycyclopentyl)methyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
331	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxycyclopentyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.4
332	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxy-2-methylpropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4
333	1,5-anhydro-3-((2-((trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)-2,3-dideoxypentitol			623.5

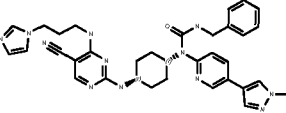
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Ex. No.	IUPAC name	structural formula	salt	MS
334	3-benzyl-1-(trans-4-((5-cyano-4-(((1-hydroxycyclohexyl)methyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			635.5

[Table 1-67]

Ex. No.	IUPAC name	structural formula	salt	MS
335	3-benzyl-1-(trans-4-((5-cyano-4-(((1-hydroxycyclobutyl)methyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.4
336	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxypropyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			581.4
337	3-benzyl-1-(trans-4-((5-cyano-4-((3-hydroxy-3-methylbutan-2-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.5
338	1,5-anhydro-2-((2-((trans-4-((benzylcarbamoyl) (5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)-2,4-dideoxypentitol			623.5
339	3-benzyl-1-(trans-4-((5-cyano-4-((2-methoxyethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			581.5

[Table 1-68]

Ex. No.	IUPAC name	structural formula	salt	MS
340	3-benzyl-1-(trans-4-((5-cyano-4-((3-(1H-imidazol-1-yl)propyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			631.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
341	1-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)piperidine-3-carboxamide			634.5
342	N-(2-((2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)ethyl)acetamide			
343	3-benzyl-1-(trans-4-((5-cyano-4-((3-(2-oxopyrrolidin-1-yl)propyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			648.5
344	3-benzyl-1-(trans-4-((5-cyano-4-(4-(ethylsulfonyl)-piperazin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			

[Table 1-69]

Ex. No.	IUPAC name	structural formula	salt	MS
345	3-benzyl-1-(trans-4-((5-cyano-4-((2-methoxyethyl)(methyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			595.4
346	3-benzyl-1-(trans-4-((5-cyano-4-((2-(pyrrolidin-1-yl)-ethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.6
347	4-(((2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)methyl)benzenesulfonamide			692.4
348	3-benzyl-1-(trans-4-((5-cyano-4-((2R,6S)-2,6-dimethylmorpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
349	3-benzyl-1-(trans-4-((5-cyano-4-((2-thienylmethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			619.4

[Table 1-70]

Ex. No.	IUPAC name	structural formula	salt	MS
350	3-benzyl-1-(trans-4-((5-cyano-4-(5-oxo-1,4-diazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.5
351	3-benzyl-1-(trans-4-((5-cyano-4-(3-(methylsulfonyl)pyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			655.5
352	3-benzyl-1-(trans-4-((5-cyano-4-((2-(methylsulfonyl)ethyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			629.4
353	3-benzyl-1-(trans-4-((5-cyano-4-((2-(1H-1,2,4-triazol-1-yl)ethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			618.4
354	3-benzyl-1-(trans-4-((5-cyano-4-(((1,5-dimethyl-1H-pyrazol-3-yl)-methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			631.5

[Table 1-71]

Ex. No.	IUPAC name	structural formula	salt	MS
355	3-benzyl-1-(trans-4-((5-cyano-4-(((2,5-dimethyl-3-furyl)methyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			631.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
356	1,5-anhydro-2-((2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)amino)-2,4-dideoxy-D-threo-pentitol			623.5
357	3-benzyl-1-(trans-4-((5-cyano-4-((3-fluoro-propyl)amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			583.4
358	3-benzyl-1-(trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-azetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			611.4
359	3-benzyl-1-(trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-pyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			625.5

[Table 1-72]

Ex. No.	IUPAC name	structural formula	salt	MS
360	3-benzyl-1-(trans-4-((5-cyano-4-(3-((dimethyl(oxide)-lambda ⁶ -sulfanylidene)amino)pyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			668.5
361	3-benzyl-1-(trans-4-((5-cyano-4-((5-oxopyrrolidin-3-yl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			606.5
362	3-benzyl-1-(trans-4-((5-cyano-4-(1-(methylimino)-1-oxide-lambda ⁴ ,4-thiazinan-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			654.5
363	3-benzyl-1-(trans-4-((5-cyano-4-((4-oxo-5-azaspiro[2.4]hepta-7-yl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
364	3-benzyl-1-(trans-4-((5-cyano-4-(3-((dimethyl (oxide)-lambda ⁶ -sulfanylidene)amino)azetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			654.5

[Table 1-73]

Ex. No.	IUPAC name	structural formula	salt	MS
365	3-benzyl-1-(trans-4-((5-cyano-4-(4-((dimethyl (oxide)-lambda ⁶ -sulfanylidene)amino)piperidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			682.5
366	3-benzyl-1-(trans-4-((5-cyano-4-(1-methylhexahydropyrrolo-[3,4-b]pyrrole-5(1H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.6
367	3-benzyl-1-(trans-4-((5-cyano-4-((1,1-dioxidetetrahydrothiophen-3-yl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			641.4
368	3-benzyl-1-(trans-4-((5-cyano-4-(5-methylhexahydropyrrolo-[3,4-b]pyrrole-1(2H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.5
369	3-benzyl-1-(trans-4-((5-cyano-4-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			653.4

[Table 1-74]

Ex. No.	IUPAC name	structural formula	salt	MS
370	3-benzyl-1-(trans-4-((5-cyano-4-(1,1-dioxide-1,4-thiazepan-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			655.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
371	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxabicyclo[4.2.0]octa-7-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
372	3-benzyl-1-(trans-4-((5-cyano-4-(4-fluoropiperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.4
373	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxo-1,7-diazaspiro[4.4]nona-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
374	3-benzyl-1-(trans-4-((5-cyano-4-((oxetan-3-ylmethyl)amino)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4

[Table 1-75]

Ex. No.	IUPAC name	structural formula	salt	MS
375	3-benzyl-1-(trans-4-((5-cyano-4-(4-(trifluoromethyl)-piperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			659.5
376	3-benzyl-1-(trans-4-((5-cyano-4-((3,3-difluorocyclobutyl)-amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			611.2
377	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxidethiomorpholin-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			625.4
378	3-benzyl-1-(trans-4-((5-cyano-4-(1,1-difluoro-5-azaspiro[2.4]hept-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			639.5

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
379	3-benzyl-1-(trans-4-((5-cyano-4-(3,4-dihydro-2,7-naphthyridine-2(1H)-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			640.5

[Table 1-76]

Ex. No.	IUPAC name	structural formula	salt	MS
380	3-benzyl-1-(trans-4-((5-cyano-4-(3,4-dihydro-2,6-naphthyridine-2(1H)-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			640.4
381	3-benzyl-1-(trans-4-((5-cyano-4-(3-methoxypyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.5
382	3-benzyl-1-(trans-4-((5-cyano-4-(3-cyanopyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
383	3-benzyl-1-(trans-4-((5-cyano-4-((3aR,7aR)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridin-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
384	3-benzyl-1-(trans-4-((5-cyano-4-((tetrahydro-2H-pyran-3-yl)methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5

[Table 1-77]

Ex. No.	IUPAC name	structural formula	salt	MS
385	3-benzyl-1-(trans-4-((5-cyano-4-((tetrahydro-2H-pyran-2-ylmethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.6
386	3-benzyl-1-(trans-4-((5-cyano-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
387	3-benzyl-1-(trans-4-((5-cyano-4-(thiomorpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.4
388	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylpyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			607.5
389	3-benzyl-1-(trans-4-((5-cyano-4-((2S)-2-(methoxymethyl)-pyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5

[Table 1-78]

Ex. No.	IUPAC name	structural formula	salt	MS
390	3-benzyl-1-(trans-4-((5-cyano-4-((2R)-2-(methoxymethyl)-pyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			621.5
391	N-(1-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)pyrrolidin-3-yl)-N-ethylacetamide			662.6
392	3-benzyl-1-(trans-4-((5-cyano-4-(4-methyl-1,4-diazepan-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.6

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
393	3-benzyl-1-(trans-4-((5-cyano-4-((3-ethoxypropyl)amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.5
394	3-benzyl-1-(trans-4-((5-cyano-4-((thietan-3-ylmethyl)amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.4

[Table 1-79]

Ex. No.	IUPAC name	structural formula	salt	MS
395	3-benzyl-1-(trans-4-((5-cyano-4-((2-hydroxy-2-methylpropyl)-(methyl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.5
396	3-benzyl-1-(trans-4-((5-cyano-4-((3-methoxypropyl)-(methyl)amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.5
397	3-benzyl-1-(trans-4-((5-cyano-4-((2S,3S)-3-(2-hydroxypropan-2-yl)-2-methylpyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			649.6
398	3-benzyl-1-(trans-4-((5-cyano-4-((2R,3R)-3-(2-hydroxypropan-2-yl)-2-methylpyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			649.6
399	3-benzyl-1-(trans-4-((5-cyano-4-((2S,3S)-3-hydroxy-2-methyl-3-(trifluoromethyl)pyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			675.4

[Table 1-80]

Ex. No.	IUPAC name	structural formula	salt	MS
400	3-benzyl-1-(trans-4-((5-cyano-4-((2S,3R)-3-cyclopropyl-3-hydroxy-2-methylpyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.6
401	3-benzyl-1-(trans-4-((5-cyano-4-((pyrrolidin-2-ylmethyl)amino)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea trifluoroacetate		CF ₃ C OOH	606.5
402	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5
403	3-benzyl-1-(trans-4-((5-cyano-4-(3-oxa-9-azaspiro[5.5]undeca-9-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			661.5
404	3-benzyl-1-(trans-4-((5-cyano-4-(7-oxa-2-azaspiro[3.5]nona-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5

[Table 1-81]

Ex. No.	IUPAC name	structural formula	salt	MS
405	3-benzyl-1-(trans-4-((5-cyano-4-(7-oxa-1-azaspiro[3.5]nona-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
406	3-benzyl-1-(trans-4-((5-cyano-4-(8-oxo-2,7-diazaspiro[4.4]nona-2-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.5
407	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxa-1-azaspiro[3.4]octa-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			619.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
408	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxa-1-azaspiro[3.5]nona-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
409	3-benzyl-1-(trans-4-((5-cyano-4-(2,2-dioxide-2-thia-7-azaspiro[4.5]deca-7-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			695.5

[Table 1-82]

Ex. No.	IUPAC name	structural formula	salt	MS
410	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.5]nona-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5
411	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			619.5
412	3-benzyl-1-(trans-4-((5-cyano-4-(1-oxa-7-azaspiro[4.5]deca-7-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.6
413	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-7-azaspiro[4.5]deca-7-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			647.5
414	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-7-azaspiro[4.4]nona-7-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.5

[Table 1-83]

Ex. No.	IUPAC name	structural formula	salt	MS
415	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.3]hepta-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			605.5
416	3-benzyl-1-(trans-4-((5-cyano-4-(2,5-dioxa-8-azaspiro[3.5]nona-8-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			635.5
417	3-benzyl-1-(trans-4-((5-cyano-4-(6-oxa-1-azaspiro[3.3]hepta-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			605.5
418	3-benzyl-1-(trans-4-((5-cyano-4-(4-fluoro-2-methoxyphenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.5
419	3-benzyl-1-(trans-4-((5-cyano-4-(6-hydroxypyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			601.4

[Table 1-84]

Ex. No.	IUPAC name	structural formula	salt	MS
420	3-benzyl-1-(trans-4-((5-cyano-4-(2-hydroxypyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			601.4
421	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			654.5
422	3-benzyl-1-(trans-4-((5-cyano-4-(imidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			624.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
423	1-(trans-4-((4-(1,2-benzothiazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			641.4
424	1-(trans-4-((4-(1,2-benzothiazol-6-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			641.4

[Table 1-85]

Ex. No.	IUPAC name	structural formula	salt	MS
425	3-benzyl-1-(trans-4-((5-cyano-4-(4-oxo-3,4-dihydroquinazolin-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			650.3
426	3-benzyl-1-(trans-4-((5-cyano-4-phenylpyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			584.4
427	3-benzyl-1-(trans-4-((5-cyano-4-(4-fluorophenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
428	3-benzyl-1-(trans-4-((5-cyano-4-(4-cyanophenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.4
429	3-benzyl-1-(trans-4-((5-cyano-4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			668.4

[Table 1-86]

Ex. No.	IUPAC name	structural formula	salt	MS
430	N-(3-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)phenyl)acetamide			641.4
431	4-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)benzamide			627.4
432	3-benzyl-1-(trans-4-((5-cyano-4-(4-(dimethylamino)phenyl)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			627.4
433	3-benzyl-1-(trans-4-((5-cyano-4-(pyridin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			585.4
434	3-benzyl-1-(trans-4-((4-(4-chlorophenyl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			618.4

[Table 1-87]

Ex. No.	IUPAC name	structural formula	salt	MS
435	1-(trans-4-((4-(4-acetylphenyl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			626.4
436	3-benzyl-1-(trans-4-((5-cyano-4-(2-methoxypyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
437	3-benzyl-1-(trans-4-((5-cyano-4-(3-fluoro-phenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4

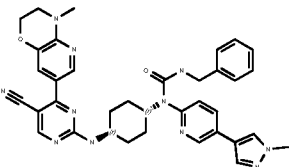
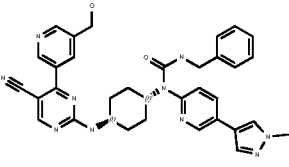
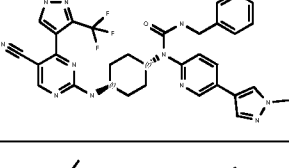
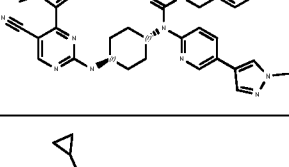
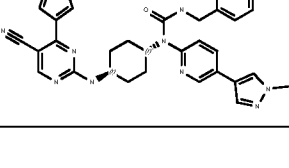
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
438	3-benzyl-1-(trans-4-((5-cyano-4-(2-fluoro-phenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
439	3-benzyl-1-(trans-4-((5-cyano-4-(3-cyanophenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			609.4

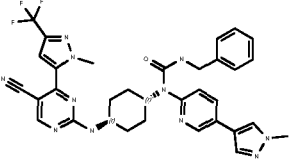
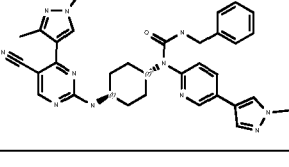
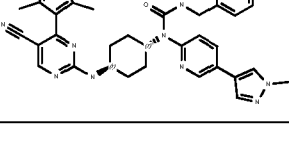
[Table 1-88]

Ex. No.	IUPAC name	structural formula	salt	MS
440	3-benzyl-1-(trans-4-((5-cyano-4-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			663.3
441	3-benzyl-1-(trans-4-((5-cyano-4-(6-(hydroxymethyl)pyridin-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
442	3-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)benzenesulfonamide			663.4
443	4-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)benzenesulfonamide			661.3
444	1-(trans-4-((4-(2,1,3-benz-oxadiazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			626.4

[Table 1-89]

Ex. No.	IUPAC name	structural formula	salt	MS
445	3-benzyl-1-(trans-4-((5-cyano-4-(4-methyl-3,4-dihydro-2H-pyrido-[3,2-b][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			656.4
446	3-benzyl-1-(trans-4-((5-cyano-4-(5-(hydroxymethyl)pyridin-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
447	3-benzyl-1-(trans-4-((5-cyano-4-(3-(trifluoromethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			640.4
448	3-benzyl-1-(trans-4-((5-cyano-4-(1,3-dimethyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
449	3-benzyl-1-(trans-4-((5-cyano-4-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			628.4

[Table 1-90]

Ex. No.	IUPAC name	structural formula	salt	MS
450	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			656.4
451	3-benzyl-1-(trans-4-((5-cyano-4-(1,3-dimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
452	3-benzyl-1-(trans-4-((5-cyano-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			616.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
453	3-benzyl-1-(trans-4-((5-cyano-4-(2,4-dimethyl-1,3-thiazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			619.4
454	3-benzyl-1-(trans-4-((5-cyano-4-(2-methyl-1,3-benzoxazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			639.4

[Table 1-91]

Ex. No.	IUPAC name	structural formula	salt	MS
455	3-benzyl-1-(trans-4-((5-cyano-4-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			667.5
456	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
457	3-benzyl-1-(trans-4-((5-cyano-4-(3,5-dimethyl-1,2-oxazol-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			603.4
458	3-benzyl-1-(trans-4-((5-cyano-4-(2-methoxypyridin-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.4
459	3-benzyl-1-(trans-4-((5-cyano-4-(1,5-dimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4

[Table 1-92]

Ex. No.	IUPAC name	structural formula	salt	MS
460	ethyl(4-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)-1H-pyrazol-1-yl)acetate			660.4
461	3-(4-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)-1H-pyrazol-1-yl)propanamide			645.5
462	3-benzyl-1-(trans-4-((5-cyano-4-(1-(difluoromethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			624.4
463	3-benzyl-1-(trans-4-((4-(1-benzyl-1H-pyrazol-4-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			664.5
464	2-(4-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)-1H-pyrazol-1-yl)acetamide			631.4

[Table 1-93]

Ex. No.	IUPAC name	structural formula	salt	MS
465	3-benzyl-1-(trans-4-((5-cyano-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			658.5
466	3-benzyl-1-(trans-4-((5-cyano-4-(pyrazolo[1,5-a]pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			624.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
467	methyl 2-(2-((trans-4-((benzylcarbamoyl)(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)amino)cyclohexyl)amino)-5-cyanopyrimidin-4-yl)-1H-indole-6-carboxylate			681.4
468	3-benzyl-1-(trans-4-((5-cyano-4-(1,5-dimethyl-1H-pyrazol-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4
469	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			588.4

[Table 1-94]

Ex. No.	IUPAC name	structural formula	salt	MS
470	3-benzyl-1-(trans-4-((5-cyano-4-(3-(trifluoromethyl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			640.4
471	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-indazol-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			638.5
472	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-1H-pyrazol-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			588.5
473	3-benzyl-1-(4-((5-cyano-4-(1H-imidazol-2-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			574.4
474	3-benzyl-1-(trans-4-((5-cyano-4-(pyridin-2-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			585.4

[Table 1-95]

Ex. No.	IUPAC name	structural formula	salt	MS
475	3-benzyl-1-(trans-4-((5-cyano-4-(pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			585.4
476	3-benzyl-1-(trans-4-((5-cyano-4-(6-methylpyridazin-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			600.4
477	3-benzyl-1-(trans-4-((5-cyano-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			656.4
478	3-benzyl-1-(trans-4-((5-cyano-4-((3S)-3-cyano-3-cyclopropyl-2-oxopyrrolidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			656.5
479	3-benzyl-1-(trans-4-((5-cyano-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			658.4

[Table 1-96]

Ex. No.	IUPAC name	structural formula	salt	MS
480	3-benzyl-1-(trans-4-((5-cyano-4-(3-methoxyazetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
481	3-benzyl-1-(trans-4-((5-cyano-4-(3-(hydroxymethyl)azetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
482	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
483	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			603.2
484	3-benzyl-1-(trans-4-((5-cyano-2-(oxetan-3-yloxy)pyrimidin-4-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			580.4

[Table 1-97]

Ex. No.	IUPAC name	structural formula	salt	MS
485	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-yloxy)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			580.4
486	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			645.4
487	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			618.4
488	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			620.5
489	3-benzyl-1-(trans-4-((5-cyano-4-(5,6-dihydro[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			629.4

[Table 1-98]

Ex. No.	IUPAC name	structural formula	salt	MS
490	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea			645.4
491	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			646.4
492	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			642.3
493	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			639.4
494	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			614.3

[Table 1-99]

Ex. No.	IUPAC name	structural formula	salt	MS
495	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			616.3
496	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea			641.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
497	3-benzyl-1-(trans-4-((5-chloro-4-((2-(isopropylsulfonyl)-phenyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			713.4
498	1-(trans-4-((4-(1,3-benzothiazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			640.4
499	1-(trans-4-((4-(1,3-benzothiazol-6-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			640.4

[Table 1-100]

Ex. No.	IUPAC name	structural formula	salt	MS
500	3-benzyl-1-(trans-4-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			545.4
501	3-benzyl-1-(trans-4-((5-cyano-4-((2-(isopropylsulfonyl)-phenyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			702.4
502	3-benzyl-1-(trans-4-((4-chloro-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			541.4
503	3-benzyl-1-(trans-4-((5-cyano-4-(morpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.4
504	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)cyclohexyl)-1-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			536.3

[Table 1-101]

Ex. No.	IUPAC name	structural formula	salt	MS
505	3-benzyl-1-(trans-4-((5-cyanopyridin-2-yl)amino)-cyclohexyl)-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			524.3
506	3-benzyl-1-(trans-4-((5-cyano-4-(5,6-dihydro[1,2,4]triazolo-[4,3-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			630.5
507	3-benzyl-1-(trans-4-((5-cyano-4-(3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			698.5
508	3-benzyl-1-(trans-4-((5-cyano-4-(5,7-dihydro-6H-pyrrolo-[3,4-b]pyridin-6-yl)pyrimidin-2-yl)amino) cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			626.4
509	3-benzyl-1-(trans-4-(((4-(((5-tert-butyl-1,3-oxazol-2-yl)methyl)amino)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.5

[Table 1-102]

Ex. No.	IUPAC name	structural formula	salt	MS
510	3-benzyl-1-(trans-4-((5-cyano-4-((1H-pyrazol-5-yl)methyl)-amino)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			603.5
511	3-benzyl-1-(trans-4-((5-cyano-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			617.4

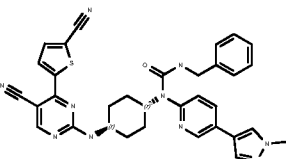
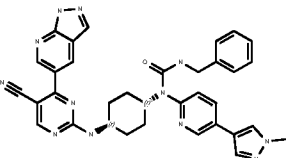
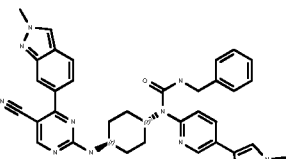
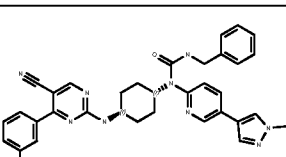
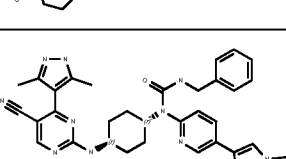
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
512	3-benzyl-1-(trans-4-((5-cyano-4-((1,3-thiazol-2-yl)methyl)-amino)pyrimidin-2-yl)amino)- cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			620.5
513	3-benzyl-1-(trans-4-((5-cyano-4-(7-oxabicyclo[2.2.1]hepta-2-ylamino)pyrimidin-2-yl)amino)- cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			619.4
514	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-4-oxoimidazolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			606.5

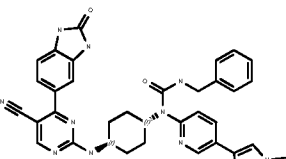
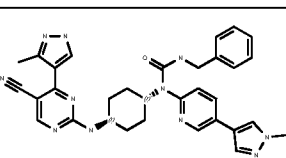
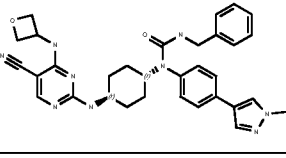
[Table 1-103]

Ex. No.	IUPAC name	structural formula	salt	MS
515	3-benzyl-1-(trans-4-((5-cyano-4-(1,3-oxazolidin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			579.4
516	3-benzyl-1-(trans-4-((5-cyano-4-(((3,3-difluorocyclobutyl)-methyl)amino)pyrimidin-2-yl)amino) cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl) urea			627.4
517	3-benzyl-1-(trans-4-((5-cyano-4-(spiro[2.2]penta-1-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			589.5
518	1-(trans-4-((4-(adamantan-1-ylamino)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			657.5
519	3-benzyl-1-(trans-4-((5-cyano-4-(methylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl) pyridin-2-yl)urea			537.4

[Table 1-104]

Ex. No.	IUPAC name	structural formula	salt	MS
520	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			615.3
521	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazolo[3,4-b]pyridin-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			625.4
522	3-benzyl-1-(trans-4-((5-cyano-4-(2-methyl-2H-indazol-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			638.5
523	3-benzyl-1-(trans-4-((5-cyano-4-(3-(morpholin-4-yl-sulfonyl)phenyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			733.5
524	3-benzyl-1-(trans-4-((5-cyano-4-(3,5-dimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			602.4

[Table 1-105]

Ex. No.	IUPAC name	structural formula	salt	MS
525	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			640.4
526	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			588.4
527	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			576.1

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
528	3-benzyl-1-(trans-4-((5-cyano-4,5'-bipyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			610.3
529	3-benzyl-1-(trans-4-((5-cyano-4-(piperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			591.5

[Table 1-106]

Ex. No.	IUPAC name	structural formula	salt	MS
530	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea			605.4
531	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxopyrrolidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			591.4
532	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			580.4
533	3-benzyl-1-(trans-4-((5-cyano-4-(1-methyl-2-oxo-1,8-diazaspiro[4.5]deca-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			674.4
534	3-benzyl-1-(trans-4-((5-cyano-4,5'-bipyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			587.3

[Table 1-107]

Ex. No.	IUPAC name	structural formula	salt	MS
535	3-benzyl-1-(trans-4-((5-cyano-4,5'-bipyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			585.3
536	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			608.2
537	3-benzyl-1-(trans-4-((5-cyano-4-(1,1-dioxide-thiomorpholin-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			640.4
538	3-benzyl-1-(trans-4-((5-cyano-4-(5-cyano-2-thienyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			616.3
539	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			578.3

[Table 1-108]

Ex. No.	IUPAC name	structural formula	salt	MS
540	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)urea			587.4
541	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			620.4

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
542	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			589.4
543	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			606.3
544	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl)urea			575.3

[Table 1-109]

Ex. No.	IUPAC name	structural formula	salt	MS
545	1-benzyl-3-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-methyl-3-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			633.4
546	3-benzyl-1-(trans-4-((5-cyano-4-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			689.3
547	3-benzyl-1-(trans-4-((5-cyano-4-(4-methyl-5-oxo-1,4-diazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			634.4
548	3-benzyl-1-(trans-4-((5-cyano-4-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			690.3

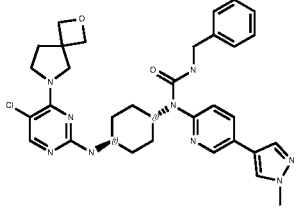
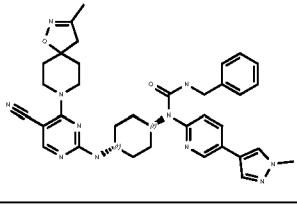
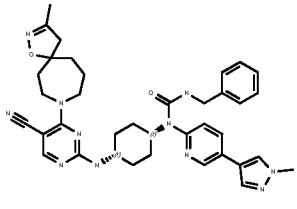
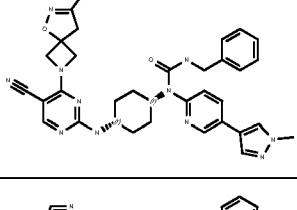
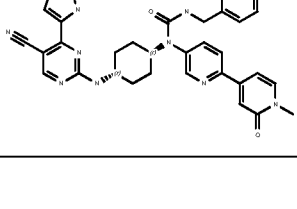
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
549	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			614.4

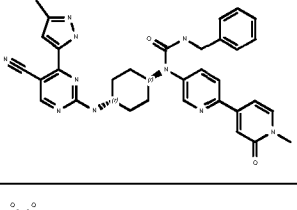
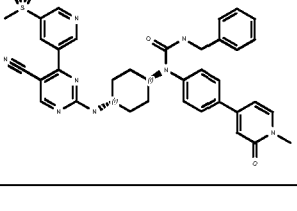
[Table 1-110]

Ex. No.	IUPAC name	structural formula	salt	MS
550	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)urea			600.3
551	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			575.3
552	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			589.4
553	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			607.3
554	3-benzyl-1-(trans-4-((5-cyano-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			647.3

[Table 1-111]

Ex. No.	IUPAC name	structural formula	salt	MS
555	3-benzyl-1-(trans-4-((5-chloro-4-(2-oxa-6-azaspiro[3.4]octa-6-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			628.3
556	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-oxa-2,8-diazaspiro[4.5]deca-2-en-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			660.4
557	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-oxa-2,8-diazaspiro[4.6]undeca-2-en-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			674.4
558	3-benzyl-1-(trans-4-((5-cyano-4-(7-methyl-5-oxa-2,6-diazaspiro[3.4]octa-6-en-2-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			632.3
559	3-benzyl-1-(trans-4-((5-cyano-4-(1H-pyrazol-5-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			601.3

[Table 1-112]

Ex. No.	IUPAC name	structural formula	salt	MS
560	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(1'-methyl-2'-oxo-1',2'-dihydro-2,4'-bipyridin-5-yl)urea			615.3
561	3-benzyl-1-(trans-4-((5-cyano-4-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)urea			689.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
562	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-oxa-2,7-diazaspiro[4.4]nona-2-en-7-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			646.4
563	3-benzyl-1-(5-bromopyrimidin-2-yl)-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)urea			578.2
564	3-benzyl-1-(trans-4-((4-(5,6-dihydro[1,2,4]triazolo-[1,5-a]pyrazine-7(8H)-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea hydrochloride		HCl	673.3

[Table 1-113]

Ex. No.	IUPAC name	structural formula	salt	MS
565	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			608.3
566	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-6-azaspiro[3.4]octa-6-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			662.4
567	3-benzyl-1-(trans-4-((4-(3,4-dihydro-2,6-naphthyridine-2(1H)-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			683.3
568	1-benzyl-3-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-3-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-methylurea			621.4
569	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-oxa-2,8-diazaspiro[4.6]undeca-2-en-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			674.4

[Table 1-114]

Ex. No.	IUPAC name	structural formula	salt	MS
570	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1-oxa-2,8-diazaspiro[4.6]undeca-2-en-8-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			674.4
571	N-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenylazetidine-1-carboxamide			633.4
572	1-benzyl-3-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-ethyl-3-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			635.4
573	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(1-methyl-1H-indazol-6-yl) urea			550.2
574	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl) urea			622.3

[Table 1-115]

Ex. No.	IUPAC name	structural formula	salt	MS
575	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea			580.3
576	1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl) urea			608.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
577	3-benzyl-1-(trans-4-((5-cyano-4-(5-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			616.3
578	3-benzyl-1-(trans-4-((5-cyano-4-(3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			617.3
579	1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyrimidin-2-ylmethyl) urea			609.3

[Table 1-116]

Ex. No.	IUPAC name	structural formula	salt	MS
580	1-benzyl-3-(trans-4-((5-cyano-4-(5-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-3-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-methylurea			630.4
581	benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl) amino) cyclohexyl) (5-(2-methoxypyrimidin-5-yl) pyridin-2-yl)carbamate			608.3
582	1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl) amino)cyclohexyl)-3-(2-fluorobenzyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			625.3
583	3-benzyl-1-(3-chloro-2-methyl-2H-pyrazolo[3,4-b]pyridin-5-yl)-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)urea			585.2
584	3-benzyl-1-(trans-4-((5-cyano-4-(1,4-oxazepan-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			636.4

[Table 1-117]

Ex. No.	IUPAC name	structural formula	salt	MS
585	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)pyrimidin-2-yl)urea			650.3
586	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(2-methyl-2H-pyrazolo[3,4-c]pyridin-5-yl)urea			553.3
587	N-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide			608.3
588	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			651.2
589	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			650.3

[Table 1-118]

Ex. No.	IUPAC name	structural formula	salt	MS
590	3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)-1-(trans-4-((4-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			651.3
591	3-benzyl-1-(trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			693.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
592	3-benzyl-1-(trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			692.3
593	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)urea			551.2
594	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)urea			551.2

[Table 1-119]

Ex. No.	IUPAC name	structural formula	salt	MS
595	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			649.3
596	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			650.3
597	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)-4-methylpyridin-2-yl)urea			621.3
598	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-4,6-dimethyl-5,5'-bipyrimidin-2-yl)urea			636.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
599	benzyl (trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl)pyrimidin-2-yl) amino) cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			650.3

[Table 1-120]

Ex. No.	IUPAC name	structural formula	salt	MS
600	benzyl (trans-4-((4-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			683.2
601	3-benzyl-1-(trans-4-((4-(3-fluoro-3-(hydroxymethyl)-azetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			683.2
602	benzyl (trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			693.4
603	benzyl (trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-azetidin-1-yl)pyrimidin-2-yl)amino) cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) carbamate			640.3
604	3-benzyl-1-(trans-4-((5-cyano-4-(3-fluoro-3-(hydroxymethyl)-azetidin-1-yl)pyrimidin-2-yl)amino) cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			640.3

[Table 1-121]

Ex. No.	IUPAC name	structural formula	salt	MS
605	3-benzyl-1-(trans-4-((5-cyano-4-((3-methyloxetan-3-yl) amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			593.2

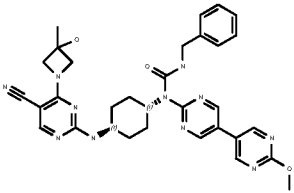
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
606	3-benzyl-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			652.2
607	3-benzyl-1-(trans-4-((5-cyano-4-((3-methyloxetan-3-yl)amino)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			622.2
608	benzyl (trans-4-((5-cyano-4-(oxetan-3-ylamino)pyrimidin-2-yl) amino) cyclohexyl) (2'-methoxy-5,5'-bipyrimidin-2-yl) carbamate			609.2
609	3-benzyl-1-(trans-4-((5-cyano-4-(oxetan-3-yloxy) pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			608.2

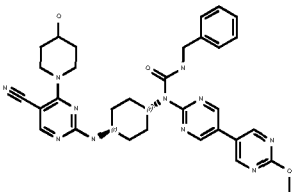
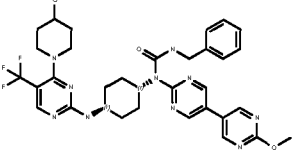
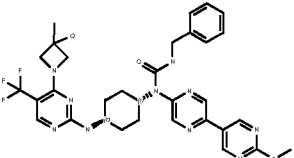
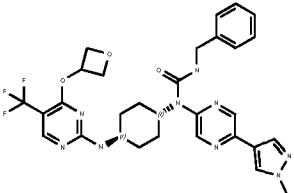
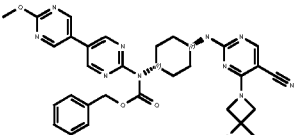
[Table 1-122]

Ex. No.	IUPAC name	structural formula	salt	MS
610	1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(pyridin-2-ylmethyl)urea			652.2
611	benzyl (trans-4-((5-cyano-4-(4-hydroxyazepan-1-yl) pyrimidin-2-yl) amino) cyclohexyl) (2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate			651.2
612	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl) pyrimidin-2-yl)amino)cyclohexyl)urea			652.2
613	3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			665.2

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
614	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			622.2

[Table 1-123]

Ex. No.	IUPAC name	structural formula	salt	MS
615	3-benzyl-1-(trans-4-((5-cyano-4-(4-hydroxypiperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			636.3
616	3-benzyl-1-(trans-4-((4-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			679.2
617	3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			665.2
618	3-benzyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-1-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			624.2
619	benzyl (trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate			623.1

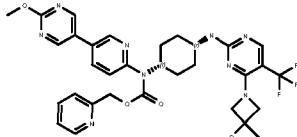
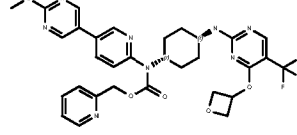
[Table 1-124]

Ex. No.	IUPAC name	structural formula	salt	MS
620	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			622.3
621	3-benzyl-1-(trans-4-((5-cyano-4-(4-fluoro-4-(hydroxymethyl)-piperidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			668.3
622	pyridin-2-ylmethyl (trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl) carbamate			667.2
623	N-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-2-phenoxyacetamide			665.2
624	pyridin-2-ylmethyl (trans-4-((4-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(2'-methoxy-5,5'-bipyrimidin-2-yl)carbamate			681.3

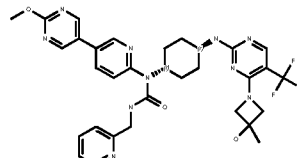
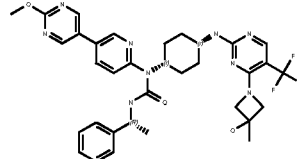
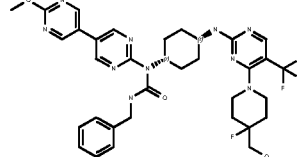
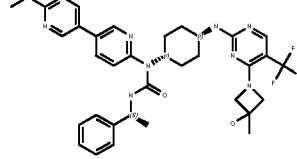
[Table 1-125]

Ex. No.	IUPAC name	structural formula	salt	MS
625	3-benzyl-1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			664.3
626	3-benzyl-1-(trans-4-((5-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			621.3
627	N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-N-(trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-phenoxyacetamide			652.2

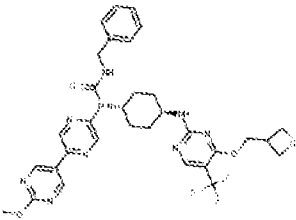
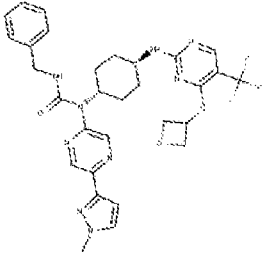
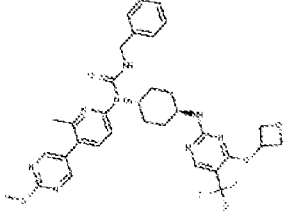
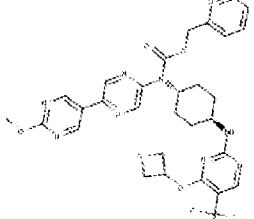
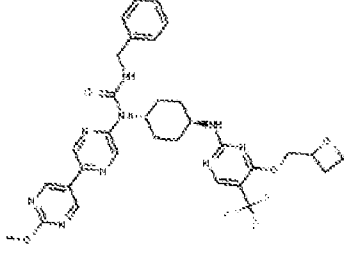
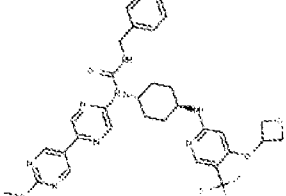
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
628	pyridin-2-ylmethyl (trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)-pyrimidin-2-yl) amino)-cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			666.2
629	pyridin-2-ylmethyl (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) (trans-4-((4-(oxetan-3-yloxy)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl) carbamate			653.3

[Table 1-126]

Ex. No.	IUPAC name	structural formula	salt	MS
630	1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(pyridin-2-ylmethyl)urea			665.3
631	1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1R)-1-phenylethyl)urea			678.3
632	3-benzyl-1-(trans-4-((4-(4-fluoro-4-(hydroxymethyl) piperidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino) cyclohexyl)-1-(2'-methoxy-5,5'-bipyrimidin-2-yl)urea			711.3
633	1-(trans-4-((4-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-((1S)-1-phenylethyl)urea			678.2

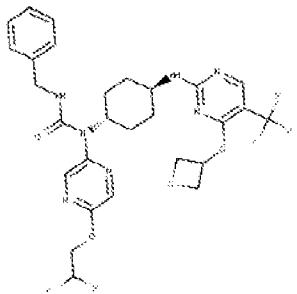
[Table 1-127]

Ex. No.	IUPAC name	structural formula	salt	MS
634	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)methoxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			666.3
635	3-benzyl-1-(5-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)urea			624.3
636	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)-6-methylpyridin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			665.3
637	(pyridin-2-yl)methyl (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl) (trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) carbamate			654.3
638	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-2-yl)methoxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			666.3
639	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyridin-2-yl)amino)cyclohexyl)urea			651.3

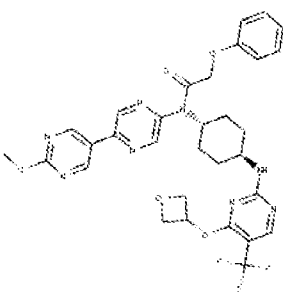
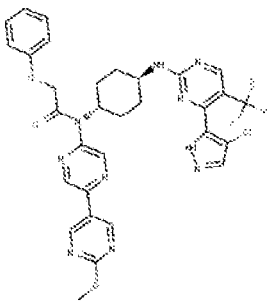
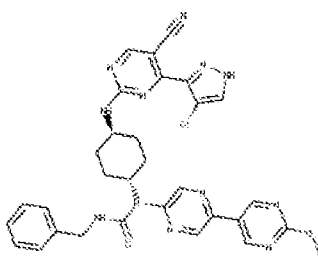
[Table 1-128]

Ex. No.	IUPAC name	structural formula	salt	MS
640	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((3-methyloxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			666.3
641	3-((1S)-2-methoxy-1-phenylethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			696.3
642	3-((1R)-2-methoxy-1-phenylethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			696.3
643	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-5-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			680.2
644	3-benzyl-1-(5-(2-methoxyethoxy)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			618.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
645	3-benzyl-1-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			624.2

[Table 1-129]

Ex. No.	IUPAC name	structural formula	salt	MS
646	N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-N-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-phenoxyacetamide			653.2
647	N-(trans-4-((4-(4-chloro-1H-pyrazol-5-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-2-phenoxyacetamide			681.2
648	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			637.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
649	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(4-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			636.3
650	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(6-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			636.3
651	3-benzyl-1-(5-(2-methoxy-pyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(2-oxo-1,8-diazaspiro[4.5]decan-8-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			732.4

[Table 1-130]

Ex. No.	IUPAC name	structural formula	salt	MS
652	3-benzyl-1-(1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-4-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			640.3
653	5-((benzylcarbamoyl) (trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-amino)-N-(2-methoxyethyl)-pyrazine-2-carboxamide			645.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
654	3-benzyl-1-(trans-4-((4-(cyclobutylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			649.3
655	3-benzyl-1-(trans-4-((4-(3,6-dihydro-2H-pyran-4-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			662.3
656	3-benzyl-1-(trans-4-((4-((cyclobutylmethyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			663.3
657	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			575.3

[Table 1-131]

Ex. No.	IUPAC name	structural formula	salt	MS
658	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3,3-dimethylurea			575.2
659	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide			574.2

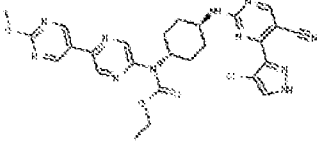
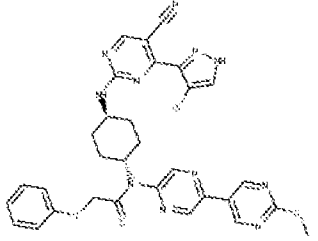
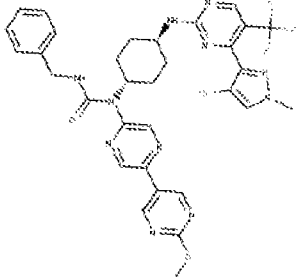
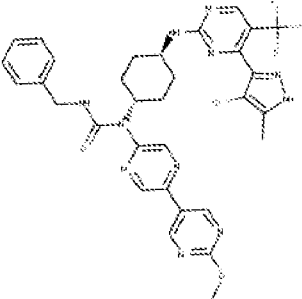
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Ex. No.	IUPAC name	structural formula	salt	MS
660	3-((5-((benzylcarbamoyl) (trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)amino)pyrazin-2-yl)oxy)-N-methylpropanamide			645.3
661	3-benzyl-1-(5-bromopyrazin-2-yl)-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)urea			607.1
662	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(4-methyl-1H-pyrazol-5-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			660.3
663	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(1-methyl-1H-pyrazol-4-yl)urea			531.2

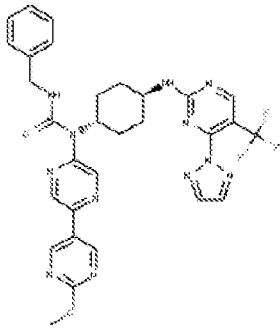
[Table 1-132]

Ex. No.	IUPAC name	structural formula	salt	MS
664	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-(2-methoxyethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			605.3
665	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-(3-methoxypropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			619.4

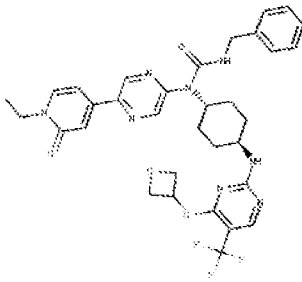
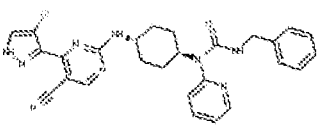
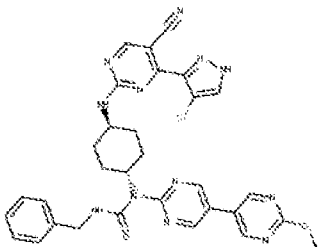
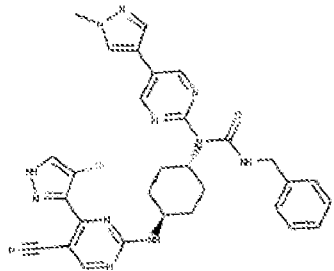
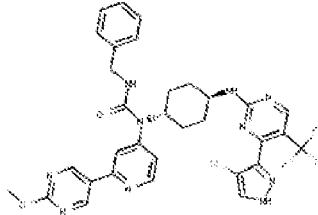
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
666	ethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			576.2
667	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-2-phenoxyacetamide			638.3
668	3-benzyl-1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			694.3
669	3-benzyl-1-(trans-4-((4-(4-chloro-5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			694.2

[Table 1-133]

Ex. No.	IUPAC name	structural formula	salt	MS
670	3-benzyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			647.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
671	3-benzyl-1-(5-(1-ethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			665.3
672	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-pyridin-2-ylurea			528.2
673	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy(5,5'-bipyrimidin)-2-yl)urea			637.3
674	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)urea			609.3
675	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2-(2-methoxypyrimidin-5-yl)pyridin-4-yl)urea			679.2

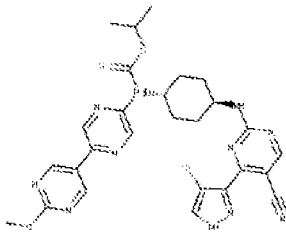
[Table 1-134]

Ex. No.	IUPAC name	structural formula	salt	MS
676	3-benzyl-1-(trans-4-((4-(4-bromo-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			724.2
677	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(1-methyl-1H-pyrazol-3-yl)urea			574.2
678	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			636.3
679	(pyridin-2-yl)methyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			638.3
680	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy(2,5'-bipyrimidin)-4-yl)urea			680.2
681	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(2'-methoxy(4,5'-bipyrimidin)-2-yl)urea			680.2

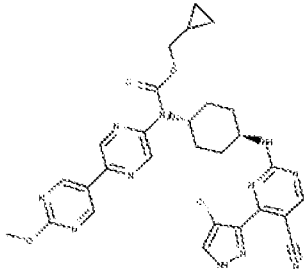
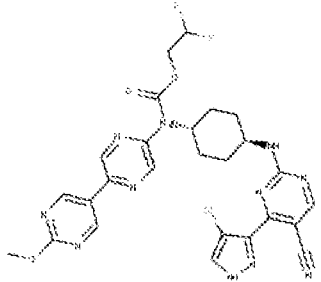
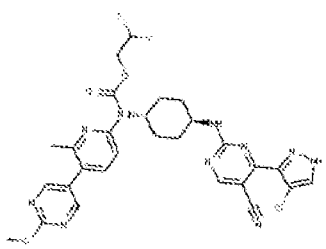
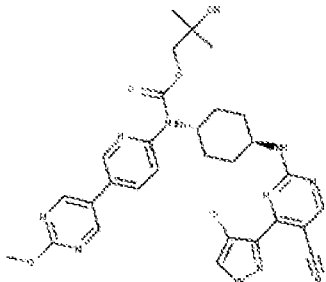
[Table 1-135]

Ex. No.	IUPAC name	structural formula	salt	MS
682	3-benzyl-1-(trans-4-((4-(4-cyclopropyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			686.3
683	3-benzyl-1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			730.3
684	1-benzyl-3-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-methylurea			651.3
685	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-propan-2-ylurea			589.3
686	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-cyclopropyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			587.2

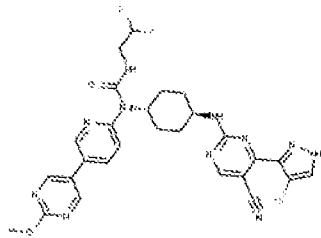
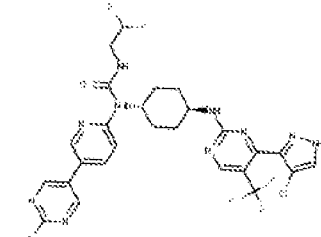
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
687	propan-2-yl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			590.2

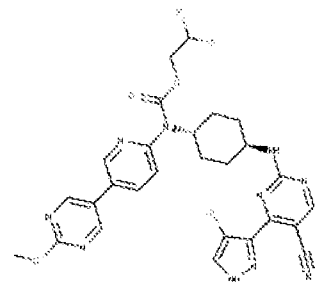
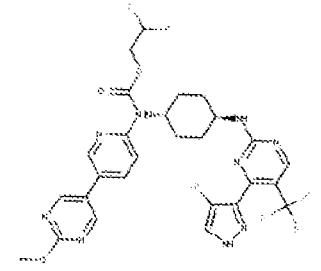
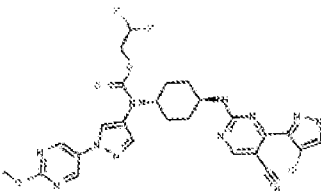
[Table 1-136]

Ex. No.	IUPAC name	structural formula	salt	MS
688	cyclopropylmethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			602.3
689	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			612.2
690	2,2-difluoroethyl(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)-6-methylpyridin-2-yl)carbamate			625.2
691	2-hydroxy-2-methylpropyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			619.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
692	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			610.2
693	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			653.3

[Table 1-137]

Ex. No.	IUPAC name	structural formula	salt	MS
694	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			611.2
695	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			654.2
696	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(1-(2-methoxypyrimidin-5-yl)-1H-pyrazol-4-yl)carbamate			600.2

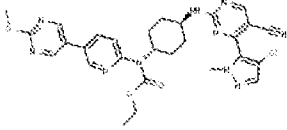
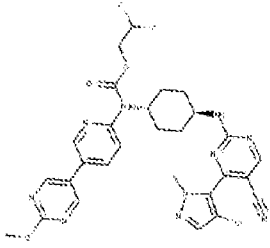
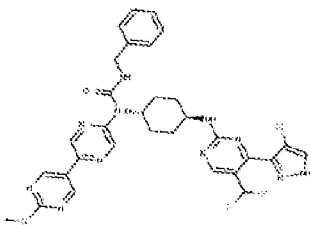
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
697	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(4-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			611.2
698	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(4-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			654.2
699	ethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			589.2

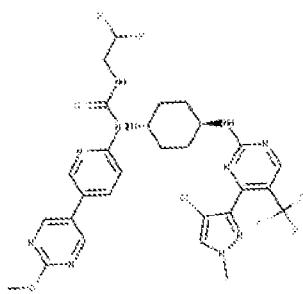
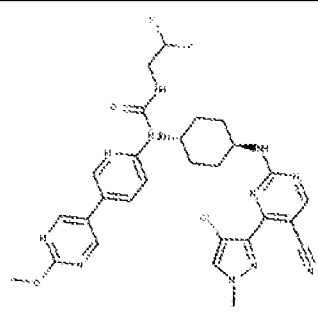
[Table 1-138]

Ex. No.	IUPAC name	structural formula	salt	MS
700	2,2-difluoroethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			625.2
701	(1-fluorocyclopropyl)methyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			662.2
702	2,2-difluoroethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			668.2

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
703	ethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			589.2
704	2,2-difluoroethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			625.2
705	3-benzyl-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(difluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			662.2

[Table 1-139]

Ex. No.	IUPAC name	structural formula	salt	MS
706	1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			667.2
707	1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			624.2

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
708	3-benzyl-1-(trans-4-((5-chloro-4-(4-chloro-1H-pyrazol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			646.2
709	2,2-difluoroethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(1-(cyclopropylmethyl)-1H-pyrazol-4-yl) carbamate			589.2
710	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			703.3
711	2,2-difluoroethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(4-(2-methoxypyrimidin-5-yl)pyridin-2-yl) carbamate			625.3

[Table 1-140]

Ex. No.	IUPAC name	structural formula	salt	MS
712	2,2-difluoroethyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(4-(2-methoxypyrimidin-5-yl)pyridin-2-yl) carbamate			668.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
713	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(6-oxa-2-azaspiro[3.4]octan-2-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			664.3
714	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(difluoromethyl)pyrimidin-2-yl) amino) cyclohexyl) -3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			635.3
715	1-(trans-4-((4-(cyclopropylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			608.3
716	3-(2,2-difluoroethyl)-1-(trans-4-((4-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			652.3
717	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			678.3

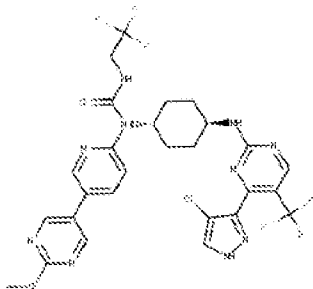
[Table 1-141]

Ex. No.	IUPAC name	structural formula	salt	MS
718	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-6-azaspiro[3.4]octan-6-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			664.3
719	3-(2,2-difluoroethyl)-1-(trans-4-((4-(3,4-dihydro-2,6-naphthyridin-2(1H)-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			685.4
720	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(2-oxa-7-azaspiro[4.4]nonan-7-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			678.3
721	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(propylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			610.3
722	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-((propan-2-yl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			610.3
723	1-(trans-4-((4-((3,3-difluorocyclobutyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			658.3

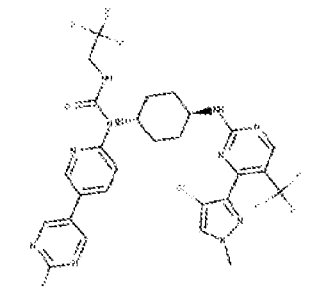
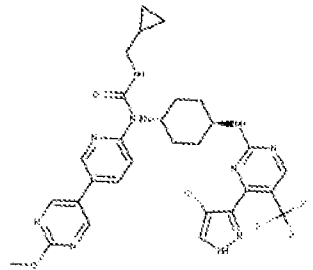
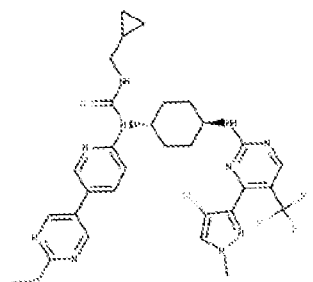
[Table 1-142]

Ex. No.	IUPAC name	structural formula	salt	MS
724	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(((1-methyl-1H-imidazol-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			662.3
725	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(1,4-oxazepan-4-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			652.3
726	3-(2,2-difluoroethyl)-1-(trans-4-((4-(4-hydroxyazepan-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			666.3
727	3-(2,2-difluoroethyl)-1-(trans-4-((4-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			674.3
728	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(5-oxa-2-azaspiro[3.4]octan-2-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			664.3

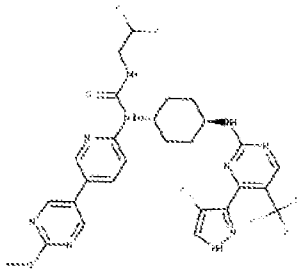
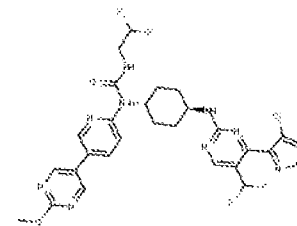
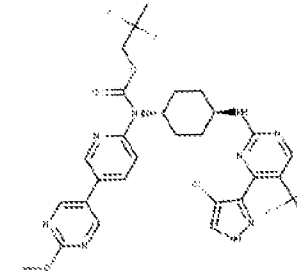
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Ex. No.	IUPAC name	structural formula	salt	MS
729	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea			671.3

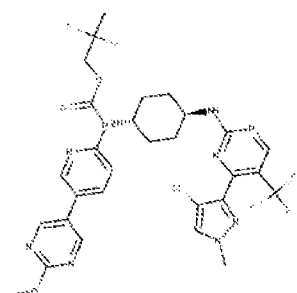
[Table 1-143]

Ex. No.	IUPAC name	structural formula	salt	MS
730	1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea			685.3
731	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(cyclopropylmethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			643.3
732	1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(cyclopropylmethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			657.3

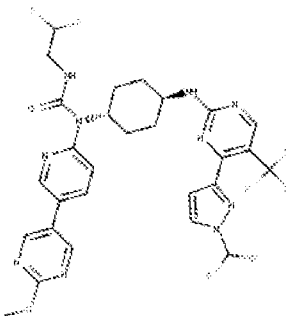
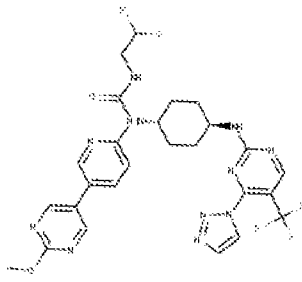
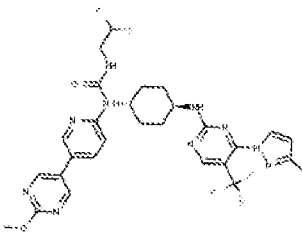
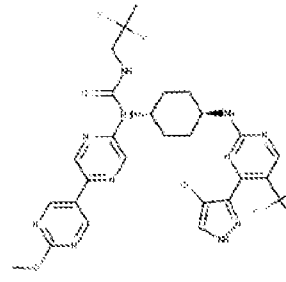
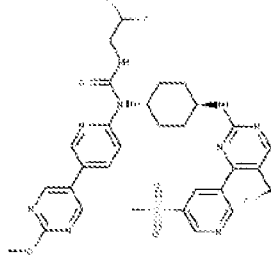
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
733	3-(2,2-difluoroethyl)-1-(trans-4-((4-(4-fluoro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) urea			637.3
734	1-(trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(difluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			649.3
735	2,2-difluoropropyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			668.2

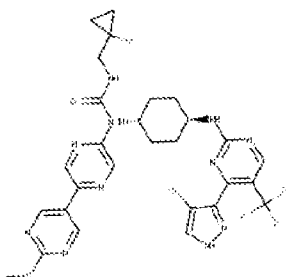
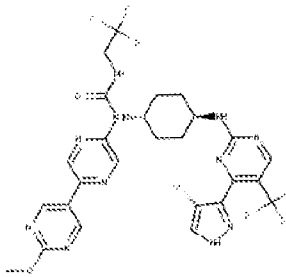
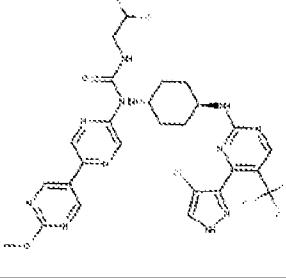
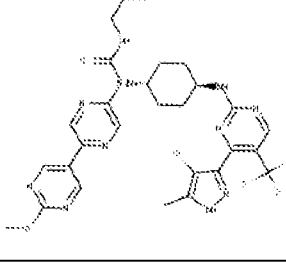
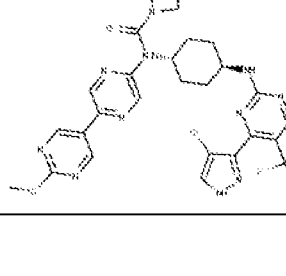
[Table 1-144]

Ex. No.	IUPAC name	structural formula	salt	MS
736	2,2-difluoropropyl (trans-4-((4-(4-chloro-1-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) carbamate			682.3

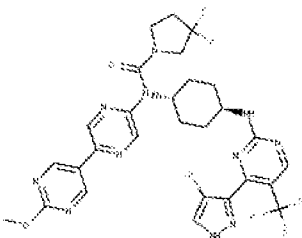
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
737	3-(2,2-difluoroethyl)-1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			669.3
738	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(1H-1,2,3-triazol-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			620.3
739	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-(3-methyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			633.3
740	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoropropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			668.3
741	3-(2,2-difluoroethyl)-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			708.3

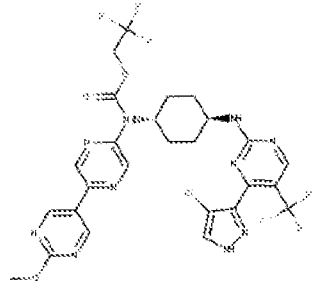
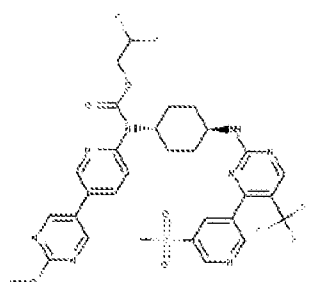
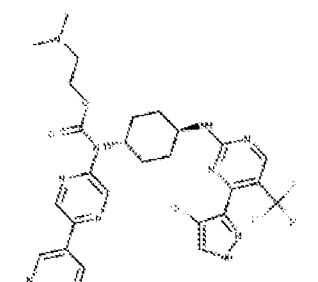
[Table 1-145]

Ex. No.	IUPAC name	structural formula	salt	MS
742	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-((1-fluorocyclopropyl)methyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			662.3
743	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			672.2
744	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			654.3
745	1-(trans-4-((4-(4-chloro-5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			668.3
746	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)-amino)cyclohexyl)-3-hydroxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-methylazetidine-1-carboxamide			660.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
747	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)-amino)cyclohexyl)-3,3-difluoro-N-(5-(2-methoxy-pyrimidin-5-yl)pyrazin-2-yl)pyrrolidine-1-carboxamide			680.3

[Table 1-146]

Ex. No.	IUPAC name	structural formula	salt	MS
748	2,2,2-trifluoroethyl(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			673.2
749	2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			709.3
750	2-(dimethylamino)ethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			662.3

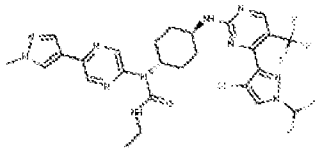
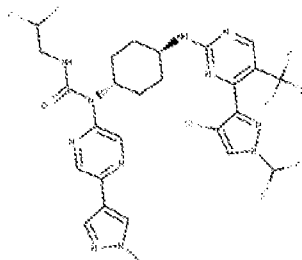
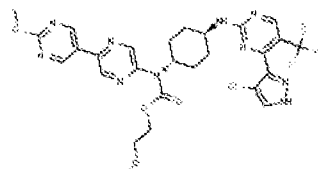
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
751	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-3,3-difluoro-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)azetidine-1-carboxamide			666.2
752	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-3-(2-methoxyethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			698.3
753	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-methoxyethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			664.3

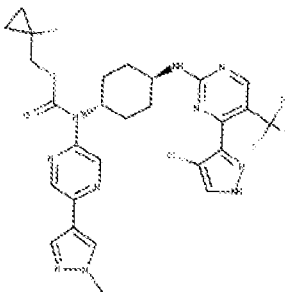
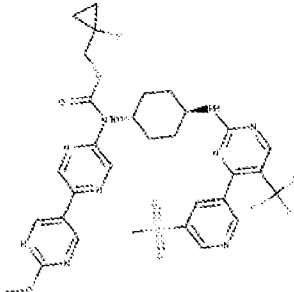
[Table 1-147]

Ex. No.	IUPAC name	structural formula	salt	MS
754	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			668.3
755	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			634.3
756	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-3-(2-methoxyethyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			670.3

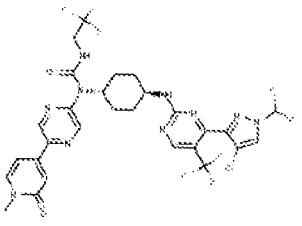
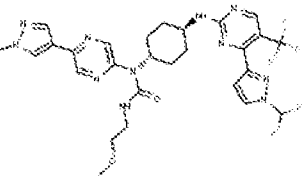
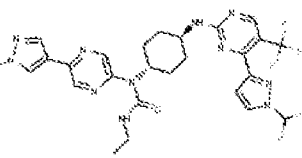
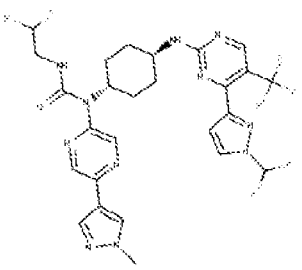
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
757	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			640.3
758	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			676.2
759	2-methoxyethyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl) amino) cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			649.3

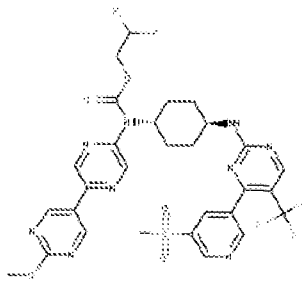
[Table 1-148]

Ex. No.	IUPAC name	structural formula	salt	MS
760	(1-fluorocyclopropyl)methyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) carbamate			635.3
761	(1-fluorocyclopropyl)methyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			718.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
762	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl) pyrazin-2-yl)-3-(2,2,2-trifluoroethyl) urea			721.2
763	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-methoxyethyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			636.3
764	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			606.3
765	3-(2,2-difluoroethyl)-1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino) cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) urea			642.3

[Table 1-149]

Ex. No.	IUPAC name	structural formula	salt	MS
766	2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			710.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
767	2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			717.3
768	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			687.3
769	(1-fluorocyclopropyl)methyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)(5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-pyrazin-2-yl)carbamate			662.2
770	(1-fluorocyclopropyl)methyl (trans-4-((4-(4-chloro-5-methyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-pyrazin-2-yl)carbamate			676.3
771	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-fluoro-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)azetidine-1-carboxamide			648.3

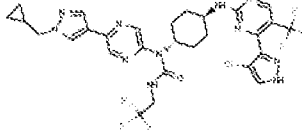
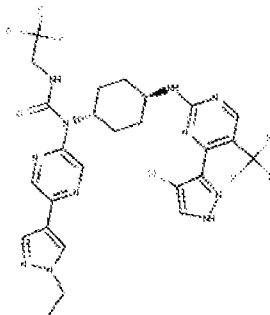
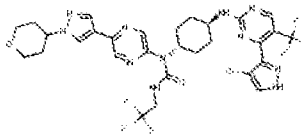
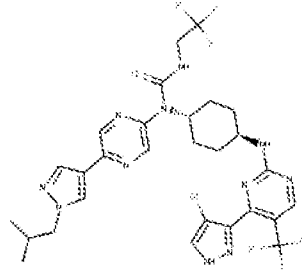
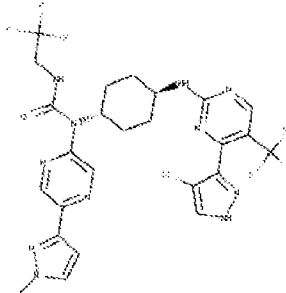
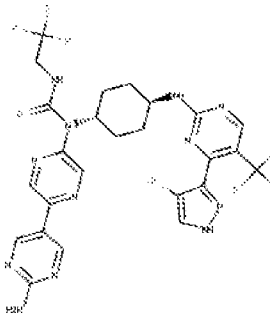
[Table 1-150]

Ex. No.	IUPAC name	structural formula	salt	MS
772	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)azetidine-1-carboxamide			630.3
773	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-3-methoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)azetidine-1-carboxamide			660.3
774	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1,3-dimethyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			658.3
775	3-(2-methoxyethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((3-methyloxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			634.3
776	3-ethyl-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((3-methyloxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			604.3
777	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((3-methyloxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			640.3

[Table 1-151]

Ex. No.	IUPAC name	structural formula	salt	MS
778	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(2-ethoxy-pyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			686.3
779	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(6-methoxy-pyridin-3-yl)-pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			671.2
780	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(pyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			642.2
781	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			670.3
782	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1,5-dimethyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			658.2
783	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(propan-2-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			672.3

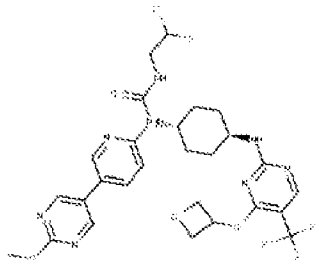
[Table 1-152]

Ex. No.	IUPAC name	structural formula	salt	MS
784	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			684.3
785	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-ethyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			658.2
786	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(oxan-4-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			714.3
787	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(2-methylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			708.3
788	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-3-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			666.2
789	1-(5-(2-aminopyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2,2-trifluoroethyl)urea			657.2

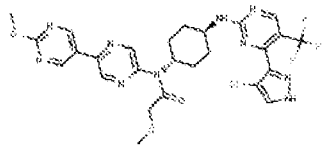
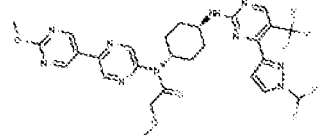
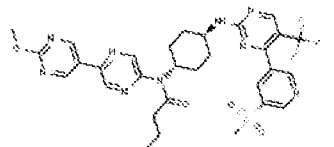
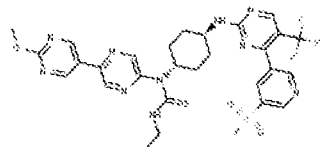
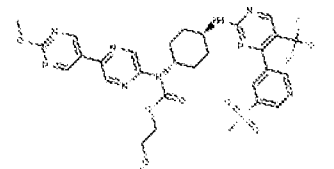
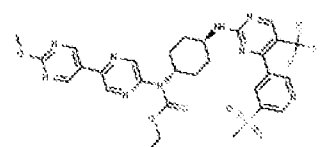
[Table 1-153]

Ex. No.	IUPAC name	structural formula	salt	MS
790	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(difluoromethyl)-1H-pyrazol-3-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			702.2
791	1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-(difluoromethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			680.2
792	1-(trans-4-((4-(4-chloro-1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl) urea			694.3
793	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			660.3
794	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			626.3

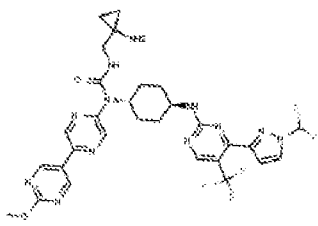
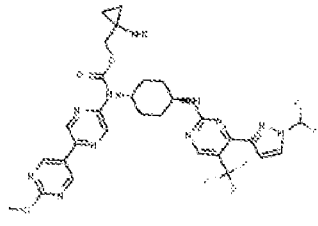
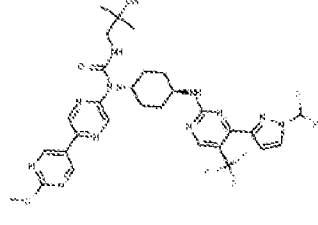
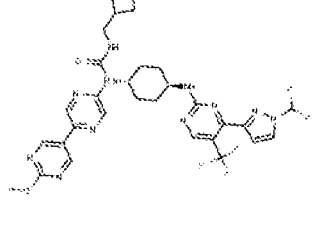
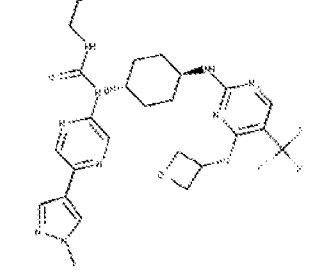
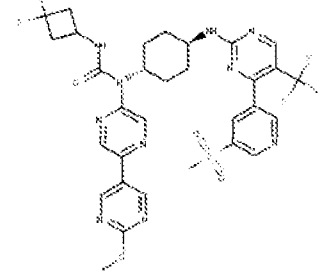
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
795	3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			625.3

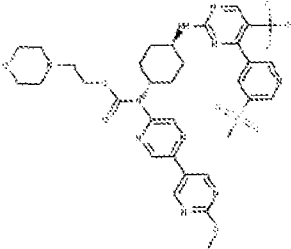
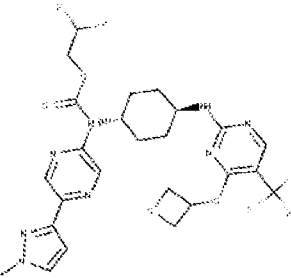
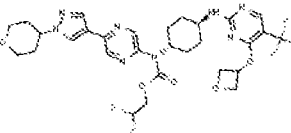
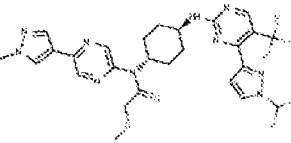
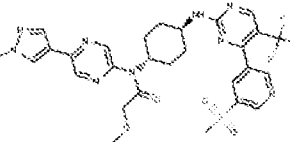
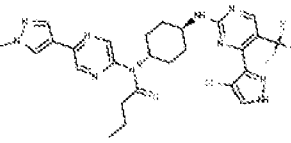
[Table 1-154]

Ex. No.	IUPAC name	structural formula	salt	MS
796	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-methoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide			619.3
797	N-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-methoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide			635.3
798	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide			672.3
799	3-ethyl-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			673.3
800	2-methoxyethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			704.2
801	ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			674.3

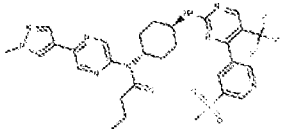
[Table 1-155]

Ex. No.	IUPAC name	structural formula	salt	MS
5 802	3-((1-aminocyclopropyl)-methyl)-1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			675.4
10 803	(1-aminocyclopropyl)methyl (trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			676.3
15 804	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl) amino) cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			678.3
20 805	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-((oxetan-3-yl)methyl)urea			676.3
25 806	3-(2,2-difluoroethyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) urea			598.3
30 807	3-(3,3-difluorocyclobutyl)-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea			735.3

[Table 1-156]

Ex. No.	IUPAC name	structural formula	salt	MS
808	2-(morpholin-4-yl)ethyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			759.4
809	2,2-difluoroethyl (5-(1-methyl-1H-pyrazol-3-yl)-pyrazin-2-yl)(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)carbamate			599.3
810	2,2-difluoroethyl (5-(1-(oxan-4-yl)-1H-pyrazol-4-yl)pyrazin-2-yl) (trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) carbamate			669.3
811	N-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-methoxy-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) acetamide			607.3
812	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-methoxy-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) acetamide			646.3
813	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) butanamide			589.2

[Table 1-157]

Ex. No.	IUPAC name	structural formula	salt	MS
814	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)butanamide			644.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
815	2-methoxy-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-N-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)acetamide			563.3
816	N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-N-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)butanamide			561.3
817	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-2-methoxy-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide			674.3
818	N-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide			617.3
819	2,2-difluoroethyl (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl) (trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)carbamate			599.3

[Table 1-158]

Ex. No.	IUPAC name	structural formula	salt	MS
820	2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate			682.2
821	2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(1-(oxan-4-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate			752.3

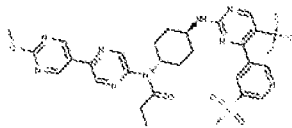
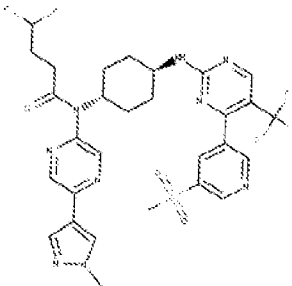
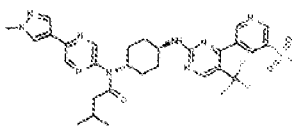
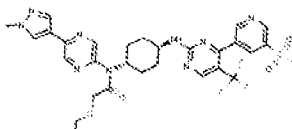
(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
822	2,2-difluoroethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-5-(1-methyl-1H-pyrazol-3-yl)-pyrazin-2-yl)carbamate			682.2
823	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoropropyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			656.3
824	3-cyclopropyl-1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea			618.3
825	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)-cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-3-propylurea			620.3

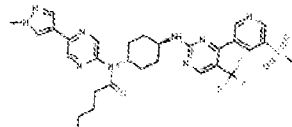
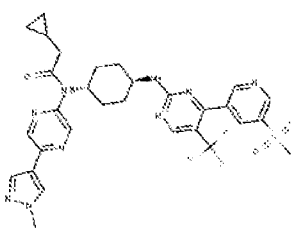
[Table 1-159]

Ex. No.	IUPAC name	structural formula	salt	MS
826	4,4-difluoro-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamide			708.3
827	2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide			688.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
828	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)propanamide			658.4
829	4,4-difluoro-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)butanamide			680.3
830	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-methyl-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)butanamide			658.3
831	2-ethoxy-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamide			660.3

[Table 1-160]

Ex. No.	IUPAC name	structural formula	salt	MS
832	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)pentanamide			658.3
833	2-cyclopropyl-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)acetamide			656.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
834	2-(dimethylamino)-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino) cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			745.4
835	3-(2,2-difluoropropyl)-1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino) cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl) urea			723.3
836	2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl) carbamate			718.3
837	2-(azetidin-1-yl)ethyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			729.3

[Table 1-161]

Ex. No.	IUPAC name	structural formula	salt	MS
838	2-hydroxy-2-methylpropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate			690.3

(continued)

Ex. No.	IUPAC name	structural formula	salt	MS
839	2-hydroxy-2-methylpropyl (trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate			651.3
840	2-hydroxy-2-methylpropyl (trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			679.3
841	2-hydroxy-2-methylpropyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			663.3
842	2-(3,3-difluoroazetidin-1-yl)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			765.3
843	2-cyclopropyl-N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)acetamide			684.3

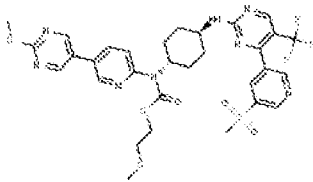
[Table 1-162]

Ex. No.	IUPAC name	structural formula	salt	MS
844	(1-aminocyclopropyl)methyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			715.3
845	propan-2-yl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			688.3
846	1-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-3-(2,2,2-trifluoroethyl)urea			727.3
847	ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			673.3
848	2-(dimethylamino)ethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			716.3
849	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea			677.3

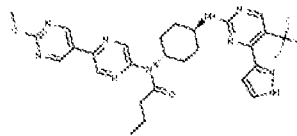
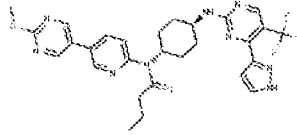
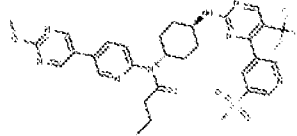
[Table 1-163]

Ex. No.	IUPAC name	structural formula	salt	MS
850	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-propylurea			647.3
851	3-cyclopropyl-1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl) amino) cyclohexyl)-1-(5-(2-methoxy-pyrimidin-5-yl)pyridin-2-yl) urea			645.3
852	1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-3-propan-2-ylurea			647.3
853	propan-2-yl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			687.3
854	(1-fluorocyclopropyl)methyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			717.3

(continued)

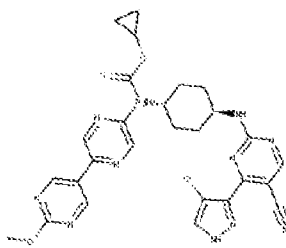
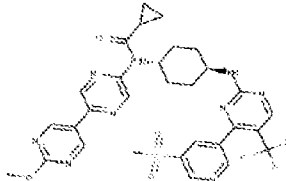
Ex. No.	IUPAC name	structural formula	salt	MS
855	2-methoxyethyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) carbamate			703.3

[Table 1-164]

Ex. No.	IUPAC name	structural formula	salt	MS
856	N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-N-(trans-4-((4-(1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)butanamide			583.3
857	N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)-N-(trans-4-((4-(1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)butanamide			582.4
858	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl) butanamide			671.3

[0472] In addition, the compounds of Reference Examples 1 - 10 in the following Tables were produced according to the methods shown in the above-mentioned Examples or a method analogous thereto. In the Tables, MS shows the measured values.

[Table 2-1]

Ref. Ex. No.	IUPAC name	structural formula	salt	MS
1	cyclopropyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			588.2
2	N-(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl) cyclo-propanecarboxamide			670.3

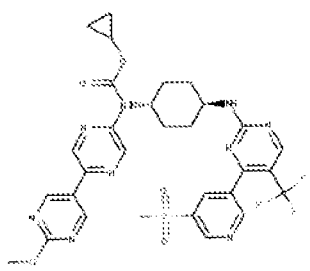
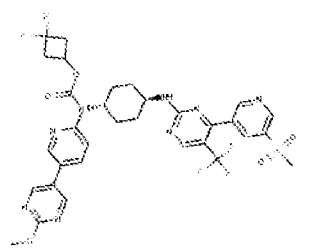
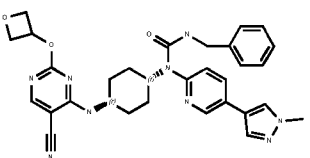
(continued)

Ref. Ex. No.	IUPAC name	structural formula	salt	MS
3	cyclopropyl (trans-4-((4-(5-(methanesulfonyl)-pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)carbamate			658.3
4	cyclopropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			685.3
5	1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)-1-(trans-4-((4-((oxetan-3-yl)oxy)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)urea			562.2
6	3,3-difluorocyclobutyl (trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-cyanopyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			637.2

[Table 2-2]

Ref. Ex. No.	IUPAC name	structural formula	salt	MS
7	3,3-difluorocyclobutyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl)amino)cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			736.3

(continued)

Ref. Ex. No.	IUPAC name	structural formula	salt	MS
8	cyclopropyl (trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate			686.3
9	3,3-difluorocyclobutyl(trans-4-((4-(5-(methanesulfonyl)pyridin-3-yl)-5-(trifluoromethyl)-pyrimidin-2-yl) amino)-cyclohexyl)(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)carbamate			735.3
10	3-benzyl-1-(trans-4-((5-cyano-2-(oxetan-3-yloxy)pyrimidin-4-yl)amino)cyclohexyl)-1-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)urea			580.4

Experimental Example 1: CDK12 binding assay

(1) Synthesis of BODIPY-FL-labeled AT-7519

[0473] To a mixture of 4-((2,6-dichlorobenzoyl)amino)-N-(piperidin-4-yl)-1H-pyrazole-3-carboxamide (AT-7519) (14.92 mg), (3-(2-((3,5-dimethyl-1H-pyrrol-2-yl-kappa-N)methylene)-2H-pyrrol-5-yl-kappa-N)propanoate) (difluoro)boron (9.5 mg), HATU (16.08 mg) and DMF (0.5 mL) was added DIPEA (0.017 mL) at room temperature, and the mixture was stirred at room temperature overnight. The mixture was purified by HPLC (water/acetonitrile, 0.1% TFA addition-based). The obtained fraction was neutralized with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure. The obtained residue was passed through a silica gel short column (methanol/ethyl acetate), and the filtrate was concentrated under reduced pressure. The obtained solid was washed with ethyl acetate/heptane (1/1) to give 4-((2,6-dichlorobenzoyl)amino)-N-(1-(3-(2-((3,5-dimethyl-1H-pyrrol-2-yl-kappa-N)methylene)-2H-pyrrol-5-yl-kappa-N)propanoyl)piperidin-4-yl)-1H-pyrazole-3-carboxamide (difluoro)boron (BODIPY-FL-labeled AT-7519) (14 mg).

(2) Confirmation of binding of CDK12 and BODIPY-FL-labeled AT-7519 by TR-FRET

[0474] Various concentrations of BODIPY-FL-labeled AT-7519 was added to an assay buffer (50 mM Hepes (pH 7.2-7.5), 10 mM MgCl₂, 1 mM EGTA, 0.01% Brij-35, 0.1 mM DTT) supplemented with His-tagged CDK12/CycK complex, terbium-labeled streptavidin (Cisbio) and biotin-labeled anti-histidine antibody (Thermo Fisher Scientific). The final concentration of CDK12/CycK complex, terbium-labeled streptavidin and biotin-labeled anti-histidine antibody was set to 2.5 nM, 0.2 nM, and 0.4 nM, respectively. After standing same for 120 min at room temperature, the fluorescence intensity derived from terbium and BODIPY-FL was measured using Envision (PerkinElmer). The signal value of each well was determined using the TR-FRET ratio calculated by the following formula.

TR-FRET ratio = (fluorescence value of BODIPY-FL) ÷ (fluorescence value of terbium)

[0475] A similar test was performed in the presence of 2 μ M AT-7519 and taken as a non-specific TR-FRET signal. It was confirmed that the BODIPY-FL-labeled AT-7519 specifically binds to CDK12 because the TR-FRET signal under conditions in the absence of AT-7519 was significantly high as compared to that in the presence of 2 μ M AT-7519 (Fig. 1).

(3) Measurement of CDK12 inhibitory activity by binding assay

[0476] His-tagged CDK12/CycK complex was added to a binding assay buffer supplemented with BODIPY-FL labeled AT-7519, terbium-labeled streptavidin and biotin-labeled anti-histidine antibody, and the mixture was stood for not less than 60 min at room temperature. This solution was added to an assay plate containing a test compound dispensed therein, and the mixture was left standing for 120 min at room temperature. The final concentration of CDK12/CycK complex, BODIPY-FL-labeled AT-7519, terbium-labeled streptavidin and biotin-labeled anti-histidine antibody was set to 2 nM, 66 nM, 0.2 nM, and 0.4 nM, respectively. The fluorescence intensity derived from terbium and BODIPY-FL was measured using Envision. The signal value of each well was determined using the TR-FRET ratio calculated by the following formula.

$$\text{TR-FRET ratio} = (\text{fluorescence value of BODIPY-FL}) \div (\text{fluorescence value of terbium})$$

[0477] The inhibitory rate (%) of the test compound against CDK12 was calculated by the following formula.

$$\text{Inhibitory rate (\%)} = (1 - (\text{TR-FRET ratio of test compound} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

[0478] The TR-FRET ratio of the CDK12 enzyme reaction mixture under compound non-addition conditions is indicated as control, and the TR-FRET ratio under 3 μ M AT-7519 addition conditions is indicated as blank.

[0479] The inhibitory rate of the test compound against CDK12 at 1 μ M is shown below.

[Table 3-1]

Example No.	1 μ M inhibitory rate (%)
199	101
319	94
440	99
469	94
482	104
483	103
485	102
492	92
495	81
527	102
530	100
532	106
536	96
538	86
539	99
542	100
552	98
553	100
566	102

(continued)

Example No.	1 μ M inhibitory rate (%)
574	103
575	101
577	88
581	88
582	91
587	102
588	99
589	100
592	101
595	104
596	103
599	102
600	83
603	76
605	90
606	96
608	98
609	99
610	103

[Table 3-2]

Example No.	1 μ M inhibitory rate (%)
611	101
614	95
619	98
620	97
623	100
625	103
626	105
627	98
628	100
629	100
630	104
631	103
633	102

(4) Measurement of CDK12 inhibitory activity by binding assay (BODIPY-FL labeled AT-7519 high concentration conditions)

[0480] His-tagged CDK12/CycK complex was blended with a binding assay buffer supplemented with BODIPY-FL labeled AT-7519, terbium-labeled streptavidin and biotin-labeled anti-histidine antibody. This solution was added to an assay plate containing a test compound dispensed therein, and the mixture was left standing for 120 min at room temperature. The final concentration of CDK12/CycK complex, BODIPY-FL-labeled AT-7519, terbium-labeled streptavidin and biotin-labeled anti-histidine antibody was set to 8 nM, 1320 nM, 0.2 nM, and 0.4 nM, respectively. The fluorescence intensity derived from terbium and BODIPY-FL was measured using Envision. The signal value of each well was determined using the TR-FRET ratio calculated by the following formula.

TR-FRET ratio = (fluorescence value of BODIPY-FL) ÷ (fluorescence value of terbium)

[0481] The inhibitory rate (%) of the test compound against CDK12 was calculated by the following formula.

Inhibitory rate (%) = $(1 - (\text{TR-FRET ratio of test compound} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$

[0482] The TR-FRET ratio of the CDK12 enzyme reaction mixture under compound non-addition conditions is indicated as control, and the TR-FRET ratio under 30 μM AT-7519 addition conditions is indicated as blank.

[0483] The inhibitory rate of the test compound against CDK12 at 1 μM is shown below.

[Table 3-3]

Example No.	1 μM inhibitory rate (%)
612	100
640	105
693	100
729	92
740	86
741	87
742	87
743	81
744	92
745	94
746	91
752	90
756	90
764	91
766	96
767	102
768	92
777	92
796	95
797	92
798	92
799	96

(continued)

Example No.	1 μ M inhibitory rate (%)
800	91
804	94
808	99
811	94
812	95
814	99
820	99
826	106
827	109
831	107
836	106
838	103
841	79
848	108
849	110
858	109

Experimental Example 2: Measurement of CDK12/CycK inhibitory activity

[0484] A test compound dissolved in DMSO was added to a reaction solution (50 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM DTT, 0.01% Tween 20, 0.01% BSA) containing CDK12/CycK enzyme and ULight-labeled eIF4E-binding protein 1 (4E-BP1) (Thr37/Thr46) peptide (PerkinElmer), and the mixture was reacted at room temperature for 60 min. The test compound was added to give an ATP solution with a final concentration of 10 μ M or 500 μ M to start the enzyme reaction, and the mixture was reacted at room temperature for 60 min. A LANCE Detection buffer (PerkinElmer) containing europium-labeled anti-phosphorylation 4E-BP1 (Thr37/Thr46) antibody (PerkinElmer) and EDTA (final concentration 10 mM) was added to discontinue the reaction. After standing for 60 min, time decomposition fluorescence value (excitation 320 nm, emission 615 nm, 665 nm) was measured by Envision (PerkinElmer). The inhibitory rate (%) of the test compound against CDK12/CyclinK was calculated by the following formula.

$$\text{Inhibitory rate (\%)} = (1 - (\text{count of test compound} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

[0485] The count of the CDK12 enzyme reaction mixture under compound non-addition conditions is indicated as control, and the count under compound non-addition and CDK12/CycK enzyme non-addition conditions is indicated as blank.

[0486] The results measured by the above-mentioned method (inhibitory rate (%) of the signal value at 1 μ M test compound relative to control is shown below.

[Table 4]

Example No.	1 μ M inhibitory rate (%)
319	98
440	101
469	103
485	103
527	99

(continued)

Example No.	1 μ M inhibitory rate (%)
530	104
536	95
539	109
553	106
566	100
574	99
575	97
577	98
581	102
582	110
588	100
589	115
596	100
600	108
603	103
605	100
608	102
609	107
610	99
611	101
614	105

Experimental Example 3: CTD pSer2 measurement using human ovarian cancer cell A2780 and In-Cell Western method

[0487] A2780 cells (ATCC) were seeded in a 96 well plate at 1.8×10^4 cells/well, and the cells were cultured overnight in a cell culture medium RPMI1640 (FUJIFILM Wako Pure Chemical Corporation) containing 10% FBS (fetal bovine serum) and 1% penicillin/streptomycin. A test compound dissolved in a cell medium was added, and the mixture was stood for 4 hr in a CO₂ incubator (37°C). The cells were fixed with ALTFIX (Falma) for 30 min, and washed 3 times with a washing buffer (20 mM Tris-HCl (pH 7.5), 500 mM NaCl, 0.1% Tween20). 0.1% Triton-X-100 diluted with PBS(-) was added and the mixture was incubated at room temperature for 15 min. Thereafter, a blocking buffer (LI-COR) was added, and the mixture was incubated at room temperature for 1 hr. An anti-CTD pS2 antibody (Abcam) suspended in an antibody diluent (blocking buffer: PBS(-)-diluted 0.1% Tween20 = 1:1) was added, and the mixture was incubated at room temperature for 1 hr. The mixture was washed 3 times with a washing buffer, IRDye800CW-labeled anti-goat antibody (LI-COR) was added, and the mixture was incubated at room temperature for 1 hr. The mixture was washed 3 times with a washing buffer, and the fluorescence wavelength at 800 nm was measured by Aeries (LI-COR).

[0488] The inhibitory rate (%) of the test compound against A2780 intracellular CTD pSer2 was calculated by the following formula.

$$\text{Inhibitory rate (\%)} = (1 - (\text{count of test compound} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

[0489] The count of the A2780 cell under compound non-addition conditions is indicated as control, and the count under compound non-addition and primary antibody non-addition conditions is indicated as blank.

[0490] The results measured by the above-mentioned method (inhibitory rate of the signal value at 1 μ M test compound relative to control) are shown below.

[Table 5]

Example No.	1 μ M inhibitory rate (%)
319	69
440	54
469	62
485	63
527	70
530	64
536	82
539	71
553	74
566	72
574	83
575	63
577	87
581	70
582	72
588	75
589	78
596	71
600	81
603	81
605	73
608	44
609	41
610	49
611	48
614	54

Experimental Example 4: In vitro proliferation suppression test

[0491] The proliferation suppressive activity of compound in A2780 cells was evaluated by the following method.

[0492] A2780 cells were seeded in a 384-well white plate at a cell density of 1,000 cells/40 μ L/well or a 96-well white plate at a cell density of 1,000 cells/90 μ L/well using an assay medium (RPMI1640 medium containing 10% fetal bovine serum (FUJIFILM Wako Pure Chemical Corporation)) and incubated at 37°C in 5% CO₂.

[0493] The next day, a test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with an assay medium, the obtained compound solution was added by 40 μ L/well or 10 μ L/well to each well of the plate containing A2780 cells and the mixture was incubated (test compound addition group). In addition, a similar reaction was performed without adding the test compound (test compound non-addition group).

[0494] Three days later, 80 μ L or 100 μ L of CellTiter-Glo reagent (Promega) was added, and the mixture was stirred for 10 min. Thereafter, the luminescence of each well was measured by ARVO-MX multilabel counter (Perkin Elmer Inc.).

[0495] The proliferation inhibitory rate (%) of each test compound against A2780 cells was calculated by the following calculation formula.

Proliferation inhibitory rate (%) = (1-luminescence of test compound addition group ÷ luminescence of test compound non-addition group) × 100

5 **[0496]** The A2780 cell proliferation inhibitory rate (%) of 1 μM test compound is shown below.

[Table 6-1]

Example No.	1 μM inhibitory rate (%)
319	97
440	98
469	97
485	97
527	97
530	97
536	91
539	96
553	98
566	98
574	97
575	99
577	94
581	99
582	97
588	98
589	97
596	99
600	93
603	93
605	98
608	99
609	99
610	98
611	97
612	97
614	94
693	98
729	98
740	96
742	96
743	95
744	97
764	95

(continued)

Example No.	1 μ M inhibitory rate (%)
766	99
767	99

[Table 6-2]

Example No.	1 μ M inhibitory rate (%)
798	99
799	99
804	96
820	99
826	98
827	99
831	99
836	99
838	98
841	99
848	99
849	97
858	99

Experimental Example 6: Antitumor action on SUM149PT CELLS tumor-bearing model

[0497] Human breast cancer cells SUM149PT were suspended in a solution of Matrigel (BD BIOSCIENCES):HBSS (Thermo Fisher Scientific)=1:1, and subcutaneously transplanted at 3×10^6 cells to the abdomen of BALB/cAJcl-nu/nu (CLEA Japan, Inc.). The tumor diameter of the engrafted tumor was measured and the tumor volume was calculated by the following formula.

$$\text{Tumor volume} = \text{major axis} \times \text{minor axis} \times \text{minor axis} \times (1/2)$$

[0498] Individuals having a tumor grown to a volume of about 120 mm³ were selected, and 5 mice per group were used for the experiment. A suspension of the test compound in 0.5% methylcellulose solution (FUJIFILM Wako Pure Chemical Corporation) was orally administered at a dose of 60 mg/kg (10 mL/kg) two times per day for 2 weeks. The tumor volume was measured over time one day before the start of the administration, and every 4 days from day 3. The next day of the completion of medication for 14 days, the tumor diameter was finally measured and the tumor volume was calculated. The tumor proliferation rate of the test compound administration group in comparison with the control administration group was taken as an average tumor volume increase ratio T/C and calculated by the following formula.

$$T/C = (\text{tumor volume of test compound administration group after completion of administration} - \text{tumor volume of test compound administration group one day before start of administration}) / (\text{tumor volume of control administration group after completion of administration} - \text{tumor volume of control administration group before start of administration}) \times 100$$

[0499] The T/C of the test compound is shown below.

[Table 7]

test compound (Example No.)	dose (mg/kg)	T/C (%)
612	60	-22

Formulation Example 1 (production of capsule)

[0500]

1) compound of Example 1	30 mg
2) finely-powdered cellulose	10 mg
3) lactose	19 mg
4) magnesium stearate	1 mg
	total 60 mg

[0501] 1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablets)

[0502]

1) compound of Example 1	30 g
2) lactose	50 g
3) cornstarch	15 g
4) calcium carboxymethylcellulose	44 g
5) magnesium stearate	1 g
1000 tablets	total 140 g

[0503] The total amount of 1), 2) and 3) and 4) (30 g) is kneaded with water, vacuum dried, and sieved. The sieved powder is mixed with 4) (14 g) and 5) (1 g), and the mixture is punched by a tableting machine, whereby 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

[Industrial Applicability]

[0504] The compound of the present invention may have a superior CDK12 inhibitory action and is expected to be useful as a prophylactic or therapeutic drug for cancer and the like.

REFERENCES CITED IN THE DESCRIPTION

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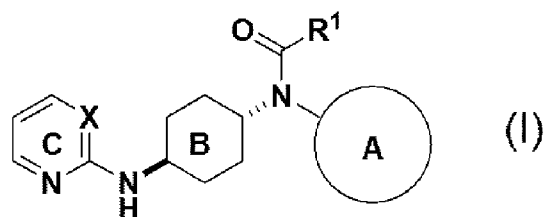
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P A T E N T K R A V

1. Forbindelse ifølge formelen (I):



hvor

5 x er CH eller N:

R^1 er eventuelt en erstattet C_{1-6} alkylgruppe, eventuelt en erstattet C_{1-6} alkoxygruppe, eventuelt en erstattet C_{6-14} arylgruppe, eventuelt en erstattet heterocyklisk gruppe, eller $-NR^2R^3$;

R^2 er et hydrogenatom eller en erstatning;

10 R^3 er en erstatning;

ring A er eventuelt en yderligere erstattet aromatisk ring;

ring B er eventuelt en yderligere erstattet cyclohexanring;

ring C er eventuelt en yderligere erstattet 6-leddet nitrogen-indeholdende aromatisk heterocykle,

15 eller et salt deraf.

2. Forbindelse ifølge krav 1, hvor

R^1 er (1) en C_{1-6} alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en eventuelt erstattet C_{6-14} arylgruppe, en eventuelt erstattet C_{6-14} aryloxygruppe og en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe, (2) en C_{1-6} alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en eventuelt erstattet C_{6-14} arylgruppe og en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe, (3) en eventuelt erstattet C_{6-14} arylgruppe, (4) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en eventuelt erstattet C_{6-14} arylgruppe eller (5) $-NR^2R^3$ [R^2 er et hydrogenatom eller en C_{1-6} alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en eventuelt erstattet C_{6-14} arylgruppe, R^3 er (i) en C_{1-6} alkylgruppe, der eventuelt er erstattet af 1 til 3 erstatninger valgt fra en eventuelt erstattet C_{3-10} cycloalkylgruppe, en eventuelt erstattet C_{6-14} arylgruppe, en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk grup-

pe og en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe eller (ii) en eventuel erstattet C₆₋₁₄ arylgruppe;

ring A er en C₆₋₁₄ aromatisk hydrocarbonring eller en 5- til 14-leddet aromatisk heterocykel, hvilke hver eventuelt er yderligere erstattet af 1 – 5 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en hydroxygruppe, (4) en eventuelt erstattet C₁₋₆ alkylgruppe, (5) en eventuelt erstattet C₂₋₆ alkenylgruppe, (6) en eventuelt erstattet C₆₋₁₄ arylgruppe, (7) en eventuelt erstattet C₁₋₆ alkoxygruppe, (8) en eventuelt erstattet aminogruppe, (9) en carboxygruppe, (10) en eventuelt erstattet carbamoylgruppe, (11) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe (den 3- til 14-leddet ikke-aromatiske heterocyklisk gruppe inkluderer også én, der har en spiro-ringstruktur) og (12) en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe;

ring B er en cyclohexanring, der ikke er yderligere erstattet; og

ring C er en pyridinring (dvs. X er CH) eller en pyrimidinring (dvs. X er N) hvilke hver eventuelt er erstattet af 1 til 3 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en eventuelt erstatte C₁₋₆ alkylgruppe, (4) en eventuelt erstattet C₆₋₁₄ arylgruppe, (5) en eventuelt erstattet C₁₋₆ alkoxygruppe, (6) en eventuelt erstattet C₆₋₁₄ aryloxygruppe, (7) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, (8) en eventuelt erstattet aminogruppe, (9) en eventuelt erstattet carbamoylgruppe, (10) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe (den 3- til 14-leddet ikke-aromatisk heterocykliske gruppe inkluderer også én, der har en bicykloringstruktur) og (11) en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe.

3. Forbindelse ifølge krav 1, hvor

R¹ er (1) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, en C₆₋₁₄ aryloxygruppe og en 5- til 14-leddet aromatisk heterocyklisk gruppe, (2) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₆₋₁₄ arylgruppe og en 5- 14-leddet aromatisk heterocyklisk gruppe, (3) en C₆₋₁₄ arylgruppe, (4) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₆₋₁₄ arylgrupper, eller (5) -NR²R³ [R² er et hydrogenatom eller en C₁₋₆ alkylgruppe,

der eventuelt er erstattet med 1 til 3 C₆₋₁₄ arylgrupper, R³ er (i) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en C₃₋₁₀ cycloalkylgruppe, (b) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en cyanogruppe, en C₁₋₆ alkoxygruppe, en C₁₋₆ alkylsulfonylgruppe og en C₁₋₆ alkylsulfonylaminogruppe, (c) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, og (d) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₁₋₆ alkylgruppe og en C₁₋₆ alkoxygruppe, eller (ii) en C₆₋₁₄ arylgruppe];

ring A er en C₆₋₁₄ aromatisk hydrocarbonring eller en 5- til 14-leddet aromatisk heterocycle, som hver eventuelt er yderligere erstattet med 1 - 5 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en hydroxygruppe, (4) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en C₁₋₆ alkoxygruppe og (c) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper, (5) en C₂₋₆ alkenylgruppe, (6) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en cyanogruppe, (c) en C₁₋₆ alkoxygruppe og (d) en carbamoylgruppe, (7) en C₁₋₆ alkoxygruppe, (8) en aminosyregruppe, der eventuelt er mono-eller di-erstatning med en eller flere erstatninger valgt fra (a) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkoxygrupper, (b) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en cyanogruppe og en C₁₋₆ alkoxygruppe, og (c) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper, (9) en carboxygruppe, (10) en carbamoylgruppe, der eventuelt er mono- eller di-erstattet med en C₁₋₆ alkylgruppe, (11) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet af 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en cyanogruppe, (c) en C₁₋₆ alkylgruppe, (d) en C₁₋₆ alkoxygruppe, (e) en C₁₋₆ alkyl-carbonylgruppe, (f) en carbamoylgruppe, (g) en mono- eller di-C₁₋₆ alkylaminogruppe og (h) en C₁₋₆ alkylsulfonylgruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkludere også én der har en spiroringstruktur) og (12) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en hydroxygruppe, en C₁₋₆ alkoxygruppe, en carbamoylgruppe, en 3- til 14-leddet ikke-aromatisk

heterocyklisk gruppe og en 5- til 14-leddet aromatisk heterocyklisk gruppe, (c) en C₁₋₆ alkoxygruppe, (d) en aminogruppe, (e) en carboxygruppe, (f) en C₁₋₆ alkoxy-carbonylgruppe, (g) en carbamoylgruppe og (h) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe;

5 ring B er en cyclohexanring, der ikke er yderligere erstattet;

ring C er en pyridinring (dvs. X er CH) eller en pyrimidinring (dvs. X er N), som hver eventuelt er yderligere erstattet med 1 til 3 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (4) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra

10 (a) et halogenatom, (b) en cyanogruppe, (c) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (d) C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (e) en mono- eller di-C₁₋₆ alkylaminogruppe, (f) en C₁₋₆ alkyl-carbonylaminogruppe, (g) en C₁₋₆ alkyl-carbonylgruppe, (h) en carbamoylgruppe, (i) en sulfamoylgruppe og (j) en 3- til 14-leddet ikke-aromatisk heterocyklisk-sulfonylgruppe, (5)

15 en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom og (b) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper, (6) en C₆₋₁₄ aryloxygruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylsulfonylgrupper, (7) en 3- til 14-leddet ikke-aromatisk heterocyklisk-oxygruppe, (8) en aminogruppe, der eventuelt er mono- eller di-erstattet med erstat-

20 ninger valgt fra (a) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (i) et halogenatom, (ii) en hydroxygruppe, (iii) en cyanogruppe, (iv) en C₃₋₁₀ cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper, (v) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₁₋₆ alkylsulfonylgruppe og en sulfamoylgruppe, (vi) en C₁₋₆ alkoxygruppe, der eventuelt er

25 erstattet med 1 til 3 halogenatomer, (vii) en mono- eller di-C₁₋₆ alkylaminogruppe, (viii) en C₁₋₆ alkyl-carbonylaminogruppe, (ix) en carbamoylgruppe, (x) en C₁₋₆ alkylsulfonylgruppe, (xi) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en oxogruppe og en C₁₋₆ alkylgruppe og (xii) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en 5- til 14-

30 leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₁₋₆ alkygruppe, en C₃₋₁₀ cycloalkylgruppe og en (C₁₋₆ alkyl) (C₁₋₆ alkyl-

sulfonyl)aminogruppe, (b) en C₃₋₁₀ cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydroxygruppe, en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper og en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 halogenatomer (C₃₋₁₀ cycloalkylgruppen inkluderer også én der har en spiroringstruktur), (c) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylsulfonylgrupper, (d) en C₃₋₁₀ cycloalkyl-carbonylgruppe, (e) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en oxogruppe, en hydroxygruppe og en C₁₋₆ alkylgruppe (den 3- til 14-leddet ikke-aromatiske heterocykliske gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruktur) og (f) en 5- til 14-leddet aromatisk heterocyklisk gruppe, (9) en carbamoylgruppe, (10) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) et halogenatom, (c) en hydroxygruppe, (d) en cyanogruppe, (e) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydroxygruppe og en C₁₋₆ alkoxygruppe, (f) en C₃₋₁₀ cycloalkylgruppe, (g) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (h) en C₁₋₆ alkyl-carbonylgruppe, (i) en carbamoylgruppe, (j) en C₁₋₆ alkylsulfonylgrupper, (k) en (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) aminogruppe, (1) en dimethyl(oxid)-λ6-sulfanylidenaminogruppe og (m) en methyliminogruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruktur) og (11) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en hydroxygruppe, (c) en cyanogruppe, (d) et halogenatom, (e) en C₁₋₆ alkylgruppe, der eventuelt er erstattet af 1 til 3 erstatninger valgt fra en hydroxygruppe, et halogenatom, en C₃₋₁₀ cycloalkylgruppe, en C₆₋₁₄ arylgruppe, en C₁₋₆ alkoxy-carbonylgruppe og en carbamoylgruppe, (f) en C₁₋₆ alkoxygruppe, (g) en C₁₋₆ alkoxy-carbonylgruppe, (h) en C₁₋₆ alkylsulfonylgrupper og (i) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe.

4. Forbindelse ifølge krav 1, hvor

R¹ er (1) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en C₆₋₁₄ arylgruppe, en C₆₋₁₄ aryloxygruppe og en 5- til 14-leddet aromatisk heterocyk-

lisk gruppe, (2) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet af 1 til 3 erstatninger valgt fra en C₆₋₁₄ arylgruppe og en 5- til 14-leddet aromatisk heterocyklisk gruppe, eller (3) - NR²R³ [R² er et hydrogenatom, og R³ er en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer og (b) en 5- til 14-leddet aromatisk heterocyklisk gruppe];

ring A er en C₆₋₁₄ aromatisk hydrocarbonring eller en 5- til 14-leddet aromatisk heterocycle som hver eventuelt yderligere er erstattet af 1 - 5 erstatninger valgt fra (a) en oxogruppe, (b) en C₁₋₆ alkylgruppe og (c) en 5- til 14-leddet aromatisk heterocyklisk gruppe eventuelt erstattet af 1 til 3 erstatninger valgt fra en C₁₋₆ alkoxygruppe;

10 ring B er en cyclohexanring ikke erstattet yderligere; og

ring C er en pyrimidinring (som er, X er N) eventuelt yderligere erstattet af 1 til 3 erstatninger valgt fra (1) en cyanogruppe, (2) en C₁₋₆ alkylgruppe eventuelt erstattet af 1 til 3 halogenatomer, (3) en 3- til 14-leddet ikke-aromatisk heterocyklisk-oxogruppe, (4) en aminogruppe eventuelt mono- eller di-erstattet af erstatning(er) valgt fra (a) en C₁₋₆ alkylgruppe eventuelt, der erstattet er med 1 til 3 hydroxygrupper og (b) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruktur), (5) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe og (c) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruktur) og (6) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en cyanogruppe, 25 (b) et halogenatom, (c) en C₁₋₆ alkylgruppe og (d) en C₁₋₆ alkylsulfonylgrupper.

5. Forbindelse ifølge krav 1, hvor

R¹ er (1) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en eventuelt erstattet C₃₋₁₀ cycloalkylgruppe, en eventuelt erstattet C₁₋₆ alkoxygruppe, en eventuelt erstattet C₆₋₁₄ arylgruppe og en eventuelt erstattet C₆₋₁₄ aryloxygruppe, (2) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstat-

ninger valgt fra et halogenatom, en hydroxygruppe, en eventuelt erstattet C₃₋₁₀ cycloalkylgruppe, en eventuelt erstattet C₁₋₆ alkoxygruppe, en eventuelt erstattet C₆₋₁₄ arylgruppe, en eventuelt erstattet aminogruppe, en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe og en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe, (3) en eventuelt erstattet C₆₋₁₄ arylgruppe, (4) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydroxygruppe, en eventuelt erstattet C₁₋₆ alkylgruppe, en eventuelt erstattet C₁₋₆ alkoxygruppe og en eventuelt erstattet C₆₋₁₄ arylgruppe eller (5) - NR²R³ [R² er et hydrogenatom eller en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra en eventuelt erstattet C₆₋₁₄ arylgruppe, og R³ er (i) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydroxygruppe, en eventuelt erstattet C₃₋₁₀ cycloalkylgruppe, en eventuelt erstattet C₁₋₆ alkoxygruppe, en eventuelt erstattet C₆₋₁₄ arylgruppe, en eventuelt erstattet aminogruppe, en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe og en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe, (ii) en eventuelt erstattet C₃₋₁₀ cycloalkylgruppe eller (iii) en eventuelt erstattet C₆₋₁₄ arylgruppe];

ring A er en C₆₋₁₄ aromatisk hydrocarbonring eller en 5- to 14-membered aromatisk heterocykle, som hver eventuelt er yderligere erstattet med 1 - 5 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en hydroxygruppe, (4) en eventuelt erstattet C₁₋₆ alkylgruppe, (5) en eventuelt erstattet C₂₋₆ alkenylgruppe, (6) en eventuelt erstattet C₆₋₁₄ arylgruppe, (7) en eventuelt erstattet C₁₋₆ alkoxygruppe, (8) en eventuelt erstattet aminogruppe, (9) en carboxygruppe, (10) en eventuelt erstattet carbamoylgruppe, (11) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en spiroringstruktur) og (12) en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe;

ring B er en cyclohexanring ikke erstattet yderligere; og

ring C er en pyridinring (dvs. X er CH) eller en pyrimidinring (dvs. X er N), som hver eventuelt er yderligere erstattet med 1 til 3 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) en eventuelt erstattet C₁₋₆ alkylgruppe, (4) en eventuelt erstattet C₆₋₁₄ arylgruppe, (5) en eventuelt erstattet C₁₋₆ alkoxygruppe, (6) en eventuelt erstattet C₆₋₁₄ aryloxygruppe, (7) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyk-

lisk-oxygruppe, (8) en eventuelt erstattet aminogruppe, (9) en eventuelt erstattet carbamoylgruppe, (10) en eventuelt erstattet 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruktur) og (11) en eventuelt erstattet 5- til 14-leddet aromatisk heterocyklisk gruppe.

6. Forbindelse ifølge krav 1, hvor

R^1 er (1) en C_{1-6} alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en C_{3-10} cycloalkylgruppe, en C_{1-6} alkoxygruppe, og en C_{6-14} aryloxygruppe, (2) en C_{1-6} alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe, (c) en C_{3-10} cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom og en aminogruppe, (d) en C_{6-14} arylgruppe, (e) en C_{1-6} alkoxygruppe, (f) en aminogruppe, der eventuelt er mono- eller di-erstattet med en C_{1-6} alkylgruppe, (g) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 halogenatomer og (h) en 5- til 14-leddet aromatisk heterocyklisk gruppe, (3) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydroxygruppe, en C_{1-6} alkylgruppe, en C_{1-6} alkoxygruppe og en C_{6-14} arylgruppe eller (4) $-NR^2R^3$ [R^2 er et hydrogenatom eller en C_{1-6} alkylgruppe, og R^3 er (i) en C_{1-6} alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe, (c) en C_{3-10} cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom og en aminogruppe, (d) en C_{1-6} alkoxygruppe, (e) en C_{6-14} arylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (f) en aminogruppe, der eventuelt er mono- eller di-erstattet med en C_{1-6} alkylgruppe, (g) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe og (h) en 5-til 14-leddet aromatisk heterocyklisk gruppe, eller (ii) en C_{3-10} cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer];

ring A er en C_{6-14} aromatisk hydrocarbonring eller en 5- til 14-leddet aromatisk heterocykle, som hver eventuelt er yderligere erstattet med 1 - 5 erstatninger valgt fra (1) et halogenatom, (2) en C_{1-6} alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom og (b) en C_{3-10} cycloalkylgruppe, (3) en C_{1-6} alkoxygruppe, der

eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en C₁₋₆ alkoxygruppe og (c) en carbamoylgruppe, der eventuelt er mono- eller di-erstattet med en C₁₋₆ alkylgruppe, (4) en carbamoylgruppe, der eventuelt er mono- eller di-erstattet med en C₁₋₆ alkylgruppe, der eventuelt er erstattet med en C₁₋₆ alkoxygruppe, (5) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en spiroringstruktur) og (6) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en C₃₋₁₀ cycloalkylgruppe og en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, (c) en C₃₋₁₀ cycloalkylgruppe, (d) en C₁₋₆ alkoxygruppe, (e) en aminogruppe, (f) en carboxygruppe, (g) en C₁₋₆ alkoxy-carbonylgruppe og (h) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe;

ring B er en cyclohexanring ikke erstattet yderligere;

ring C er en pyrimidinring, (dvs. X er N) der eventuelt yderligere er erstattet med 1 til 3 erstatninger valgt fra (1) et halogenatom, (2) en cyanogruppe, (3) C₁₋₆ alkylgruppe eventuelt erstattet af 1 til 3 halogenatomer, (4) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en cyanogruppe, (c) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (d) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (e) en mono- eller di-C₁₋₆ alkylaminogruppe, (f) en C₁₋₆ alkyl-carbonylaminogruppe, (g) en C₁₋₆ alkyl-carbonylgruppe, (h) en carbamoylgruppe, (i) en sulfamoylgruppe og (j) en 3- til 14-leddet ikke-aromatisk heterocyklisk-sulfonylgruppe, (5) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe og (c) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper, (6) en C₆₋₁₄ aryloxygruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylsulfonylgrupper, (7) en 3- til 14-leddet ikke-aromatisk heterocyklisk-oxygruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper, (8) en aminogruppe, der eventuelt er mono- eller di-erstattet med erstatninger valgt fra (a) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (i) et halogenatom, (ii) en hydroxygruppe, (iii) en cyanogruppe, (iv) en C₃₋₁₀ cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper, (v) en C₆₋₁₄ arylgruppe, der even-

tuel er erstattet med 1 til 3 erstatninger valgt fra en C₁₋₆ alkylsulfonylgrupper og en sul-
 famoylgruppe, (vi) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 halogen-
 atomer, (vii) en mono- eller di-C₁₋₆ alkylaminogruppe, (viii) en C₁₋₆ alkyl-
 carbonylaminogruppe, (ix) en carbamoylgruppe, (x) en C₁₋₆ alkylsulfonylgrupper, (xi) en 3-
 5 til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 to 3
 erstatninger valgt fra en oxogruppe og en C₁₋₆ alkylgruppe og (xii) en 5- til 14-leddet aro-
 matisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra
 en C₁₋₆ alkylgruppe, en C₃₋₁₀ cycloalkylgruppe og en (C₁₋₆ alkyl) (C₁₋₆ alkyl-sulfonyl) amino-
 gruppe, (b) en C₃₋₁₀ cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger
 10 valgt fra et halogenatom, en hydroxygruppe, en C₁₋₆ alkylgruppe, der eventuelt er erstat-
 tet med 1 til 3 hydroxygrupper og en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1
 til 3 halogenatomer (den C₃₋₁₀ cycloalkylgruppe inkluderer også én, der har en spiro-
 ringstruktur), (c) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆
 6 alkylsulfonylgrupper, (d) en C₃₋₁₀ cycloalkyl-carbonylgruppe, (e) en 3- til 14-leddet ikke-
 15 aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt
 fra en oxogruppe, en hydroxygruppe og en C₁₋₆ alkylgruppe (den 3- til 14-leddet ikke-
 aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en bro-
 formet ringstruktur, eller en spiroringstruktur) og (f) en 5- til 14-leddet aromatisk hetero-
 cyklisk gruppe, (9) en carbamoylgruppe, (10) en 3- til 14-leddet ikke-aromatisk heterocyk-
 20 lisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe,
 (b) et halogenatom, (c) en hydroxygruppe, (d) en cyanogruppe, (e) en C₁₋₆ alkylgruppe,
 der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en hydro-
 xygruppe og en C₁₋₆ alkoxygruppe, (f) en C₃₋₁₀ cycloalkylgruppe, (g) en C₁₋₆ alkoxygruppe,
 der eventuelt er erstattet med 1 til 3 halogenatomer, (h) en C₁₋₆ alkyl-carbonylgruppe, (i)
 25 en carbamoylgruppe, (j) en C₁₋₆ alkylsulfonylgrupper, (k) en (C₁₋₆ alkyl) (C₁₋₆ alkyl-
 carbonyl)aminogruppe, (1) en dimethyl(oxid)-λ6-sulfanylidenaminogruppe og (m) en
 methyliminogruppe (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer
 også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiroringstruk-
 tur) og (11) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet
 30 med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en hydroxygruppe, (c) en cyano-
 gruppe, (d) et halogenatom, (e) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3

erstatninger valgt fra en hydroxygruppe, et halogenatom, en C₃₋₁₀ cycloalkylgruppe, en C₆₋₁₄ arylgruppe, en C₁₋₆ alkoxy-carbonylgruppe og en carbamoylgruppe, (f) en C₃₋₁₀ cycloalkylgruppe, (g) en C₁₋₆ alkoxygruppe, (h) en C₁₋₆ alkoxy-carbonylgruppe, (i) en C₁₋₆ alkylsulfonylgruppe og (j) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe.

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7. Forbindelse ifølge krav 1, hvor

R¹ er (1) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra et halogenatom, en C₁₋₆ alkoxygruppe og en C₆₋₁₄ aryloxygruppe, (2) en C₁₋₆ alkoxygruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe, (c) en C₆₋₁₄ arylgruppe, (d) en aminogruppe, der eventuelt er mono- eller di-erstattet med en C₁₋₆ alkylgruppe og (e) en 5- til 14-leddet aromatisk heterocyklisk gruppe eller (3) -NR²R³ [R² er et hydrogenatom, og R³ er en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe, (c) en C₃₋₁₀ cycloalkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (d) en C₆₋₁₄ arylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer og (e) en 5- til 14-leddet aromatisk heterocyklisk gruppe];

ring A er en C₆₋₁₄ aromatisk hydrocarbonring eller en 5- to 14-leddet aromatisk heterocyklisk, som hver eventuelt er yderligere erstattet med 1 - 5 erstatninger valgt fra en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) en oxogruppe, (b) en C₁₋₆ alkylgruppe og (c) en C₁₋₆ alkoxygruppe;

ring B er en cyclohexanring ikke erstattet yderligere; og

ring C er en pyrimidinring (dvs. X er N), der eventuelt yderligere er erstattet med 1 til 3 erstatninger valgt fra (1) en cyanogruppe, (2) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer, (3) en 3- til 14-leddet ikke-aromatisk heterocyklisk-oxogruppe, (4) en aminogruppe, der eventuelt er mono- eller di-erstattet med erstatninger valgt fra (a) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper og (b) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 C₁₋₆ alkylgrupper (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicykloringstruktur, en broformet ringstruktur, eller en spiro-ringstruktur), (5) en 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger valgt fra (a) et halogenatom, (b) en hydroxygruppe og (c)

en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 hydroxygrupper (den 3- til 14-leddet ikke-aromatisk heterocyklisk gruppe inkluderer også én, der har en bicyklo-ringstruktur, en broformet ringstruktur, eller en spiroringstruktur) og (6) en 5- til 14-leddet aromatisk heterocyklisk gruppe, der eventuelt er erstattet med 1 til 3 erstatninger
 5 valgt fra (a) en cyanogruppe, (b) et halogenatom, (c) en C₁₋₆ alkylgruppe, der eventuelt er erstattet med 1 til 3 halogenatomer og (d) en C₁₋₆ alkylsulfonylgrupper.

8. Lægemiddel der omfatter forbindelsen ifølge krav 1 eller et salt deraf.

10 9. Lægemiddel ifølge krav 8 til anvendelse som en CDK12 hæmmer.

10. Lægemiddel ifølge krav 8 til anvendelse som et profylakse eller terapeutisk lægemiddel til cancer.

15 11. Forbindelse ifølge krav 1, som er 1-(trans-4-((4-(4-chloro-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2,2-difluoroethyl)-1-(5-(2-methoxypyrimidin-5-yl)pyridin-2-yl)urea eller et salt deraf.

20 12. Forbindelse ifølge krav 1, som er 1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-ethyl-1-(5-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)urea eller et salt deraf.

25 13. Forbindelse ifølge krav 1, som er N-(trans-4-((4-(5-(methansulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-N-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)butanamid eller et salt deraf.

14. Forbindelse ifølge krav 1, som er 1-(trans-4-((4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-3-(2-hydroxy-2-methylpropyl)-1-(5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)urea eller et salt deraf.

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15. Forbindelse ifølge krav 1, som er 2-hydroxy-2-methylpropyl(trans-4-((4-(5-

(methansulfonyl)pyridin-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl) (5-(2-methoxypyrimidin-5-yl)pyrazin-2-yl)carbamate eller et salt deraf.

DRAWINGS

Drawing

Fig. 1

