

# US Patent & Trademark Office

## Patent Public Search | Text View

---

United States Patent	12391674
Kind Code	B2
Date of Patent	August 19, 2025
Inventor(s)	Shinohara; Tomoichi et al.

---

### Heterocyclic compounds for the treatment of epilepsy

---

#### Abstract

The present invention provides a novel heterocyclic compound represented by Formula [I] and a salt thereof: ##STR00001## wherein the symbols are as defined in the specification, which is useful for treating, preventing and/or diagnosing seizure and the like in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), as well as a medical use therefor.

---

<b>Inventors:</b>	Shinohara; Tomoichi (Osaka, JP), Iwata; Shin (Osaka, JP), Suzuki; Masaki (Osaka, JP), Arai; Kenta (Osaka, JP), Ito; Nobuaki (Osaka, JP), Chiba; Takuya (Osaka, JP)
<b>Applicant:</b>	OTSUKA PHARMACEUTICAL CO., LTD. (Tokyo, JP)
<b>Family ID:</b>	1000008762871
<b>Assignee:</b>	OTSUKA PHARMACEUTICAL CO., LTD. (Tokyo, JP)
<b>Appl. No.:</b>	17/292528
<b>Filed (or PCT Filed):</b>	November 29, 2019
<b>PCT No.:</b>	PCT/JP2019/046879
<b>PCT Pub. No.:</b>	WO2020/111263
<b>PCT Pub. Date:</b>	June 04, 2020

#### Prior Publication Data

<b>Document Identifier</b>	<b>Publication Date</b>
US 20210403456 A1	Dec. 30, 2021

## Foreign Application Priority Data

JP 2018-224724 Nov. 30, 2018

---

## Publication Classification

**Int. Cl.:** C07D403/04 (20060101); A61P25/08 (20060101); C07D239/34 (20060101); C07D239/47 (20060101); C07D239/54 (20060101); C07D401/04 (20060101); C07D401/12 (20060101); C07D405/04 (20060101); C07D413/04 (20060101); C07D417/04 (20060101); C07D471/04 (20060101); C07D487/04 (20060101)

## U.S. Cl.:

**CPC** C07D403/04 (20130101); A61P25/08 (20180101); C07D239/34 (20130101); C07D239/47 (20130101); C07D239/54 (20130101); C07D401/04 (20130101); C07D401/12 (20130101); C07D405/04 (20130101); C07D413/04 (20130101); C07D417/04 (20130101); C07D471/04 (20130101); C07D487/04 (20130101);

## Field of Classification Search

**CPC:** C07D (403/04); C07D (239/34); C07D (239/47); C07D (239/54); C07D (401/04); C07D (401/12); C07D (405/04); C07D (413/04); C07D (417/04); C07D (471/04); C07D (487/04); A61P (25/08)

---

## References Cited

### U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
4239888	12/1979	Miller	N/A	N/A
6872729	12/2004	Shibata	544/320	A01N 43/54
10647675	12/2019	Watanabe et al.	N/A	N/A
10800758	12/2019	Shinohara et al.	N/A	N/A
2012/0202806	12/2011	Durrenberger	514/235.8	A61P 35/00
2019/0055199	12/2018	Watanabe et al.	N/A	N/A
2020/0017476	12/2019	Shinohara et al.	N/A	N/A
2020/0399245	12/2019	Shinohara et al.	N/A	N/A

### FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
1 456 964	12/1975	GB	N/A
2002-193710	12/2001	JP	N/A
2013-513564	12/2012	JP	N/A
2013-518046	12/2012	JP	N/A
2014-521651	12/2013	JP	N/A
2018-145180	12/2017	JP	N/A
6870064	12/2020	JP	N/A
2021-187859	12/2020	JP	N/A
2004/009559	12/2003	WO	N/A
2004/029204	12/2003	WO	N/A

2011/069951	12/2010	WO	N/A
2011/091153	12/2010	WO	N/A
2012/076877	12/2011	WO	N/A
2012/168710	12/2011	WO	N/A
2013/016488	12/2012	WO	N/A
2013/083994	12/2012	WO	N/A
2013/175215	12/2012	WO	N/A
2017/047602	12/2016	WO	N/A
2017/098254	12/2016	WO	N/A
2018/169360	12/2017	WO	N/A
2018/221667	12/2017	WO	N/A

## OTHER PUBLICATIONS

Mickevicius et al. (Chemistry of Heterocyclic Compounds. 2004: 40(6); 781-787). (Year: 2004). cited by examiner

International Search Report dated Mar. 5, 2020 issued in No. PCT/JP2019/046879. cited by applicant

International Preliminary Report on Patentability and Translation of Written Opinion of the International Searching Authority for PCT/JP2019/046879 dated May 25, 2021. cited by applicant  
Nilsen et al., "Discovery, Synthesis, and Optimization of Antimalarial 4(1H)-Quinolone-3-Diarylethers", Journal of Medicinal Chemistry, 2014, vol. 57, No. 9, pp. 3818-3834 (17 pages total). cited by applicant

Mickevicius et al., "Synthesis and Cyclization of N-(4-Phenoxyphenyl)- $\beta$ -Alanines", Chemistry of Heterocyclic Compounds, 2004, vol. 40, No. 6, pp. 781-787 (7 pages total). cited by applicant

International Preliminary Report on Patentability and Translation of Written Opinion of the International Searching Authority for PCT/JP2017/020322 dated Dec. 3, 2019, a priority application of U.S. Appl. No. 16/471,998 (now U.S. Pat. No. 10,800,758). cited by applicant

International Preliminary Report on Patentability and Written Opinion of the International Searching Authority for PCT/JP2018/020997 dated Dec. 3, 2019, corresponding to U.S. Appl. No. 16/471,998 (now U.S. Pat. No. 10,800,758). cited by applicant

International Search Report dated Aug. 10, 2018 issued in No. PCT/JP2018/020997, corresponding to U.S. Appl. No. 16/471,998 (now U.S. Pat. No. 10,800,758). cited by applicant

International Search Report dated Aug. 22, 2017 issued in No. PCT/JP2017/020322, a priority application of U.S. Appl. No. 16/471,998 (now U.S. Pat. No. 10,800,758). cited by applicant

Japanese Office Action issued in Application No. 2019-535398 dated Apr. 21, 2020, corresponding to U.S. Appl. No. 16/471,998 (now U.S. Pat. No. 10,800,758). cited by applicant

Office Action issued Feb. 28, 2022 in U.S. Appl. No. 17/010,182. cited by applicant

Notice of Allowance issued Oct. 3, 2022 in U.S. Appl. No. 17/010,182. cited by applicant

Simon F. Campbell, et al., "2,4-Diamino-6,7-dimethoxyquinazolines. 3. 2-(4-Heterocyclylpiperazin-1-yl) Derivatives as  $\alpha$ .SUB.1.-Adrenoceptor Antagonists and Antihypertensive Agents", Journal of Medicinal Chemistry, 1987, vol. 30, No. 10, pp. 1794-1798 (5 pages). cited by applicant

Masazumi Ikeda, et al., "Synthesis and Cytoprotective Antiulcer Activity of 2- or 4-(1H-Pyrazol-1-yl) pyrimidine Derivatives Related to Mepirizole and Dulcerazine", Chem. Pharm. Bull., vol. 44, No. 9, 1996, pp. 1700-1706 (7 pages). cited by applicant

Communication dated Aug. 30, 2023 issued by the Eurasian Patent Organization in corresponding Eurasian application No. 202191473. cited by applicant

Peereboom, R., et al., "Ring transformations in reactions of heterocyclic halogeno compounds with nucleophiles (XXXVIII). The influence of leaving group mobility on reactions of 4-X-6-methyl (or phenyl)-pyrimidine 1-oxides with liquid ammonia and with potassium amide in liquid ammonia", Recueil, Journal of the Royal Netherlands Chemical Society, Nov. 1974, vol. 93, No. 11, pp. 284-

287 (4 pages total). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. RN 1894376-77-2 Registry Entered STN: Apr. 21, 2016, Compound Name: 5-Phenoxy-2(4-piperidinyl)pyrimidine Supplier: Aurora Fine Chemicals (1 page). cited by applicant

Database Registry Chemical Abstract Service, US, STN Database accession No. RN 1891296-62-0, Apr. 17, 2016, Compound Name: 5-Phenoxy-2-(3-piperidinyl)pyrimidine Supplier: Aurora Fine Chemicals (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. RN 1045503-40-9 Registry Entered STN: Sep. 1, 2008 Compound Name: 4-Phenoxy-6-(1-piperidinyl)pyrimidine Supplier: Albany Molecular Research, Inc. (AMRI) (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. RN 1894399-87-1 Registry Entered STN: Apr. 21, 2016 Compound Name: 1-(5-Phenoxy-2-pyrimidinyl)-4-piperidinamine Supplier: Aurora Fine Chemicals ( 1 page). cited by applicant  
Bardhan, et al., "Heteroaryl Ethers by Oxidative Palladium Catalysis of Pyridotriazol-1-yloxy Pyrimidines with Arylboronic Acids", Organic Letters, 2009, vol. 11, No. 12, pp. 2511-2514 (4 pages). cited by applicant

Huang, H. et al., ACS Medicinal Chemistry Letters. 2012, vol. 3, pp. 1059-1064. cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. RN944776-58-3; STN Entry Date Aug. 16, 2007; Compound Name: 4,5-Dichloro-2-[6-(2,5-dimethylphenoxy)-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 923551-04-6; STN Entry Date Feb. 27, 2007; Compound Name: 4,5-Dichloro-2-[6-(3,5-dimethylphenoxy)-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 927639-49-4; STN Entry Date Mar. 20, 2007; Compound Name: 4,5-Dichloro-2-[6-[3-(trifluoromethoxy)phenoxy]-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 444151-95-5; STN Entry Date Aug. 19, 2002; Compound Name: 5-(2-Methoxyphenoxy)-2,2'-bipyrimidine [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 667895-27-4; STN Entry Date Mar. 26, 2004; Compound Name: Chloro-5-methoxy-2-[6-(4-methylphenoxy)-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 667895-26-3; STN Entry Date Mar. 26, 2004; Compound Name: 4-Chloro-5-ethoxy-2-[6-(4-methylphenoxy)-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 724430-57-3; STN Entry Date Aug. 9, 2004; Compound Name: 4,4,5-Dichloro-2-[6-(2-methylphenoxy)-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 724429-17-8; STN Entry Date Aug. 9, 2004; Compound Name: 4,5-Dichloro-2-[2-(3,4-dimethylphenoxy)-6-methoxy-4-pyrimidinyl]-3(2H)-pyridazinone [5] (1 page). cited by applicant

Database Registry Chemical Abstract Service, US; Retrieved from STN Database accession No. 724430-65-3; STN Entry Date Aug. 9, 2004; Compound Name: 1,5,6,7-Tetrahydro-1-[6-(2-methylphenoxy)-4-pyrimidinyl]-4H-indazol-4-one [5] ] (1 page). cited by applicant

Australian Examination Report dated Jan. 16, 2025 issued by the Australian Government in corresponding Australian application No. 2019390907. cited by applicant

Non-Final Office Action issued Feb. 10, 2025 in U.S. Appl. No. 18/091,790. cited by applicant

---

*Primary Examiner:* Carcanague; Daniel R

*Assistant Examiner:* Wilson; Jerica Katlynn

*Attorney, Agent or Firm:* Sughrue Mion, PLLC

---

## **Background/Summary**

### **CROSS REFERENCE TO RELATED APPLICATIONS**

(1) This application is a National Stage of International Application No. PCT/JP2019/046879 filed Nov. 29, 2019, claiming priority to Japanese Patent Application No. 2018-224724 filed Nov. 30, 2018.

### **TECHNICAL FIELD**

(2) The present invention relates to a heterocyclic compound and a salt thereof. The present invention also relates to a medicament having a heterocyclic compound or a salt thereof as an active ingredient and useful for treating, preventing and/or diagnosing seizure and the like in disease involving epileptic seizure or convulsive seizure.

### **BACKGROUND ART**

(3) The prevalence of epilepsy is about 1% of the population. It is considered a common neurological disorder with about 1 million patients in Japan and a lifetime morbidity rate of 3% to 4%, and it is estimated that tens of thousands of people develop epilepsy every year. About 70% of these patients can control their seizure with existing antiepileptic drugs and pursue their everyday lives without problems, but the remaining 30% of epileptic patients are unable to adequately control their seizure, and are anxious that seizure may occur without warning. Most existing antiepileptic drugs are aimed to normalize the excitation/inhibition imbalances in neural activity by suppressing hyper-excitation and excessive synchronization of neuronal activity, but doses above the optimal dose may disturb the equilibrium of neuronal activity, and induce motor dysfunction and epileptic seizure.

(4) PTL 1 discloses compounds having a pyrimidine in its structure as compounds for use in the treatment and the like of diseases or conditions requiring modulators of the Kv3.1 and/or Kv3.2 channel, including epilepsy.

(5) PTL 2 and 3 disclose compounds having a pyrimidine skeleton as kynurenine-3-monooxygenase inhibitors for treating neurodegenerative conditions including epilepsy.

(6) PTL 4 discloses a compound having a structure containing phenoxy pyrimidine or pyridyloxypyrimidine as antagonist and/or inverse agonist of cannabinoid-1 receptor, useful for the treatment of diseases including epilepsy.

### **CITATION LIST**

#### **Patent Literature**

(7) [PLT1] WO 2011/069951 [PLT2] WO 2013/016488 [PLT3] WO 2011/091153 [PLT4] WO 2004/029204

### **DISCLOSURE OF INVENTION**

#### **Solution to Problem**

(8) It is an object of the present invention to provide a novel pyrimidine compound or a salt thereof useful for treating, preventing and/or diagnosing seizure and the like in disease involving epileptic seizure or convulsive seizure, together with a medical use therefor.

(9) It is another object of the present invention to provide a medicament having a wide treatment spectrum in comparison with existing antiepileptic drugs, whereby the balance of neuronal excitation/inhibition can be maintained even at doses that completely suppress epileptic seizure.

(10) As a result of exhaustive research aimed at solving the aforementioned problems, the inventors succeeded in synthesizing a novel pyrimidine compound having a wide treatment spectrum in comparison with existing antiepileptic drugs. The present invention was perfected based on these findings.

(11) This is, the present invention includes the following embodiments.

(12) [1] A compound represented by Formula I:

(13) ##STR00002##

(14) wherein D is

(15) ##STR00003## or C.sub.1-6 alkyl optionally substituted with halogen; ring A is benzene, pyridine, indole or indazole; ring B is pyrimidine, pyridazine, pyridine, pyrazole, benzene or naphthalene, wherein, (i) when ring B is pyrimidine, ring C is selected from the group consisting of the following unsaturated rings and their oxides and dioxides (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: (a) an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 4 nitrogen atoms alone as ring-constituting heteroatom, (b) an unsaturated 7- to 15-membered bicyclic or tricyclic heterocycle containing 1 to 5 nitrogen atoms alone as ring-constituting heteroatom, (c) an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 to 3 oxygen atoms alone as ring-constituting heteroatom, (d) an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom, (e) an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom, and . . . (f) an unsaturated 3- to 8-membered monocyclic hydrocarbon ring; (ii) when ring B is pyridazine, pyridine, pyrazole, benzene or naphthalene, ring C is pyrimidine-2,4-dione or dihydropyrimidine-2,4-dione; R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —CN or —SF.sub.5; R.sup.2 is halogen, C.sub.1-6 alkyl, or —O—C.sub.1-6 alkyl; R.sup.3 is halogen, C.sub.1-6 alkyl optionally substituted with halogen or —O—C.sub.1-6 alkyl, —O—C.sub.1-6 alkyl optionally substituted with halogen, —C.sub.1-6 alkyl-OH, —OH, —CN, —CONH.sub.2 or —NH.sub.2; L is bond, C.sub.1-6 alkylene, —O— or —S—; k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0, 1 or 2, and when m is 2, each R.sup.2 independently represents the same or different substituent; and n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent; or a salt thereof.

(16) [2] The compound according to [1], wherein, in Formula I, D is

(17) ##STR00004## ring A is benzene or pyridine; ring B is pyrimidine; ring C is selected from the group consisting of the following unsaturated rings and their oxides and dioxides (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrimidine, indole, pyrrolopyridine, indazole, benzimidazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, triazolopyridine, pyrazolopyrimidine, imidazopyrimidine, triazolopyrimidine, quinoline, isoquinoline, naphthyridine, quinazoline, quinoxaline, benzodioxole, oxazine, oxazepine, benzothiazole, and benzene; R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen or —CN; R.sup.2 is —O—C.sub.1-6 alkyl; R.sup.3 is halogen, C.sub.1-6 alkyl optionally substituted with halogen or —O—C.sub.1-6 alkyl, —O—C.sub.1-6 alkyl optionally substituted with halogen, —C.sub.1-6 alkyl-OH, —OH, —CN, —CONH.sub.2 or —NH.sub.2; L is —O—; and k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0 or 1; n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent; or a salt thereof.

(18) [3] The compound according to [2], wherein, in Formula I, ring C is selected from the group consisting of the following unsaturated rings and their oxides, and those in which a part or all of

unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrrolopyridine, indazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, pyrazolopyrimidine, triazolopyrimidine, quinoline, isoquinoline, naphthyridine, quinoxaline, and benzene; R.sup.1 is halogen or C.sub.1-6 alkyl optionally substituted with halogen; R.sup.3 is C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —OH, —CONH.sub.2 or —NH.sub.2; L is —O—; k and n are 0 or 1; and m is 0; or a salt thereof.

(19) [4] The compound according to [3], wherein, in Formula I, ring C is selected from the group consisting of the following unsaturated rings and their oxides, and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrazolopyridine, and Imidazopyridine; R.sup.3 is —OH or —NH.sub.2; L is —O—; k and m are 0; and n is 0 or 1; or a salt thereof.

(20) [5] The compound according to [1], wherein, in Formula I, D is:

(21) ##STR00005## or C.sub.1-6 alkyl optionally substituted with halogen; ring A is benzene or pyridine; ring B is pyridazine, pyridine, pyrazole, benzene, or naphthalene; ring C is pyrimidine-2,4-dione or dihydropyrimidine-2,4-dione; R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with a halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —CN or —SF.sub.5; R.sup.2 is halogen, C.sub.1-6 alkyl, or —O—C.sub.1-6 alkyl; R.sup.3 is C.sub.1-6 alkyl; L is bond, C.sub.1-6 alkylene, —O— or —S—; k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0, 1 or 2, and when m is 2, each R.sup.2 independently represents the same or different substituent; and n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent; or a salt thereof.

(22) [6] The compound or salts thereof according to [5], wherein, in Formula I, ring A is benzene; ring B is benzene, pyridine, or pyridazine; ring C is dihydropyrimidine-2,4-dione; R.sup.1 is halogen; L is —O—; k is 0 or 1; and m and n are 0; or a salt thereof.

(23) [7] A compound selected from the group consisting of the following compounds:

(24) ##STR00006## ##STR00007## ##STR00008## ##STR00009## ##STR00010## ##STR00011## or a salt thereof.

(25) [8] The compound according to [7] selected from the group consisting of the following compounds:

(26) ##STR00012## ##STR00013## or a salt thereof.

(27) [9] A pharmaceutical composition comprising a compound or a salt thereof according to any of [1] to [8] as an active ingredient and pharmaceutically acceptable carrier or excipient.

(28) [10] A therapeutic, preventative and/or diagnostic agent for seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), comprising a compound or a salt thereof according to any of [1] to [8].

(29) [11] The therapeutic, preventative or diagnostic agent according to wherein the epileptic seizure is selected from focal onset seizure (also called partial seizure) with motor onset (including automatism, atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizure of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(30) [12] The therapeutic, preventative or diagnostic agent according to [10], wherein the disease involving epileptic seizure or convulsive seizure is selected from Dravet syndrome, Lennox-

Gastaut syndrome, West syndrome (epilepsia *nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.), etc.

(31) [13] A therapeutic, preventative and/or diagnostic pharmaceutical composition for seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), comprising a compound or a salt thereof according to any of [1] to [8] as an active ingredient.

(32) [14] The composition according to [13], wherein the epileptic seizure is selected from focal onset seizure (also called partial seizure) with motor onset (including automatism, atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizures of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(33) [15] The composition according to [13], wherein the disease involving epileptic seizure or convulsive seizure is selected from Dravet syndrome, Lennox-Gastaut syndrome, West syndrome (epilepsia *nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.), etc.

(34) [16] A method for treating, preventing and/or diagnosing seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), wherein comprising administering to a human in need thereof an effective amount of a compound or a salt thereof according to any of [1] to [8].

(35) [17] The method according to [16], wherein the epileptic seizure is selected from focal onset seizure (also called partial seizure) with motor onset (including automatism, atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence



seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizure of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(36) [18] The method according to [16], wherein the disease involving epileptic seizure or convulsive seizure is selected from Dravet syndrome, Lennox-Gastaut syndrome, West syndrome (epilepsia *nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.), etc.

(37) [19] A compound or a salt thereof according to any of [1] to [8] for use in the treatment, prevention and/or diagnosis of seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus).

(38) [20] The compound or a salt thereof according to [19], wherein the epileptic seizure is selected from focal onset seizure (also called partial seizure) with motor onset (including automatism, atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizure of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(39) [21] The compound or a salt thereof according to [19], wherein the disease involving epileptic seizure or convulsive seizure is selected from Dravet syndrome, Lennox-Gastaut syndrome, West syndrome (epilepsia *nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.), etc.

(40) [22] Use of a compound or a salt thereof according to any of [1] to [8] in the manufacture of a medicament for treating, preventing and/or diagnosing seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus).

(41) [23] The use according to [22], wherein the epileptic seizure is selected from focal onset seizure (also called partial seizure) with motor onset (including automatism, atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure

and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizure of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(42) [24] The use according to [22], wherein the disease involving epileptic seizure or convulsive seizure is selected from Dravet syndrome, Lennox-Gastaut syndrome, West syndrome (epilepsia *nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.), etc.

(43) The compound and a salt thereof of the present invention are highly effective for treating, preventing and/or diagnosing disease and the like involving epileptic seizure, convulsive seizure or the like. Moreover, the compound and a salt thereof of the present invention have excellent feature for use as active ingredient in pharmaceuticals, and for example have excellent feature such as few side effects, tolerability, stability (storage stability, metabolic stability, etc.) and the like.

Furthermore, the compound and a salt thereof of the present invention have a wide treatment spectrum in comparison with existing antiepileptic drugs.

---

## Description

### DESCRIPTION OF EMBODIMENTS

(1) The phrases and terms used in this specification are explained in detail below.

(2) The “C.sub.1-6 alkyl” is C.sub.1-6 linear or branched alkyl, and specific examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl and the like.

(3) C.sub.1-6 alkyl having deuterium atoms substituted for 1 to 3 hydrogen atoms is also included.

(4) The “halogen” is fluorine, chlorine, bromine, or iodine. It is preferably fluorine, chlorine, or bromine, and more preferably fluorine or chlorine.

(5) The “C.sub.1-6 alkyl optionally substituted with halogen” is linear or branched alkyl having 1 to 6 carbon atoms (C.sub.1-6) optionally substituted with 1 to 4 halogens, preferably 1 to 3 halogens, and specific examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, 3-methylpentyl, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, 2-fluoroethyl, 2-chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 1,1,2,2-tetrafluoroethyl, 3-chloropropyl, 2,3-dichloropropyl, 4,4,4-trichlorobutyl, 4-fluorobutyl, 5-chloropentyl, 3-chloro-2-methylpropyl, 5-bromohexyl, 5,6-dibromohexyl, and the like.

(6) The “C.sub.1-6 alkylene” is linear or branched alkylene having 1 to 6 carbon atoms (C.sub.1-6). Specific examples thereof include methylene, ethylene, 1-methylethylene, 2-methylethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene,

methylmethylene, ethylmethylene, dimethylmethylene, tetramethylene, pentamethylene, and hexamethylene.

(7) In addition, "C.sub.1-6 alkylene" also includes C.sub.1-6 alkylene in which 1 to 3 hydrogen atoms are substituted with deuterium atoms.

(8) Each of the groups defined in this specification may be bound appropriately to another group via a linker such as —O—, —CO—, —COO—, —S—, —SO—, —SO.sub.2—, —Si—, —O—CO— or the like.

(9) The various substituents in the compound represented by General Formula [I] of the present invention (hereafter called "compound [I] of the present invention") are explained below.

(10) D in Compound [I] of the present invention is ring A optionally substituted with (R.sup.1) k or C.sub.1-6 alkyl optionally substituted with halogen.

(11) The ring A in Compound [I] of the present invention is benzene, pyridine, indole or indazole, and is preferably benzene or pyridine.

(12) When ring B is pyrimidine, ring C in Compound [I] of the present invention is selected from the group consisting of the following unsaturated rings and their oxides and dioxides (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen; (a) an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 4 nitrogen atoms alone as ring-constituting heteroatom, (b) an unsaturated 7- to 15-membered bicyclic or tricyclic heterocycle containing 1 to 5 nitrogen atoms alone as ring-constituting heteroatom, (c) an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 to 3 oxygen atoms alone as ring-constituting heteroatom, (d) an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom, (e) an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom, and (f) an unsaturated 3- to 8-membered monocyclic hydrocarbon ring.

(13) Specific examples of an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 4 nitrogen atoms alone as ring-constituting heteroatom in the above (a) and its oxide and dioxide (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and the heterocycle in which a part or all of unsaturated bonds in its ring are reduced with hydrogen may include pyridine, piperidine, pyridine-1-oxide, pyridine-2 (1H)-one, pyrimidine, tetrahydropyrimidine, tetrahydropyrimidine-2 (1H)-one, pyridazine, pyridazine-3 (2H)-one, 4,5-dihydropyridazine, and 4,5-dihydropyridazine-3 (2H)-one.

(14) Specific examples of an unsaturated 7- to 15-membered bicyclic or tricyclic heterocycle containing 1 to 5 nitrogen atoms alone as ring-constituting heteroatom in the above (b) and its oxide and dioxide, and the heterocycle in which a part or all of unsaturated bonds in its rings are reduced with hydrogen may include indole, indoline, indoline-2-one, indoline-3-one, indoline-2,3-dione, benzimidazole (for example, 1H-benzo[d]imidazole), dihydrobenzimidazole (for example, 2,3-dihydro-1H-benzo[d]imidazole), indazole, dihydroindazole (for example, 2,3-dihydro-1H-indazole), quinoline, quinoline-2 (1H)-one, dihydroquinoline (for example, 1,2-dihydroquinoline, 3,4-dihydroquinoline), 3,4-dihydroquinolin-2 (1H)-one, tetrahydroquinoline (for example, 1,2,3,4-tetrahydroquinoline), isoquinoline, isoquinoline-1 (2H)-one, 1,3-dihydroisoquinoline, 3,4-dihydroisoquinoline, 3,4-dihydroisoquinoline-1 (2H)-one, triazolopyrimidine (for example, [1,2,4]triazolo[1,5-a]pyrimidine), triazolopyridine (for example, [1,2,3]triazolo[1,5-a]pyridine, [1,2,4]triazolo[1,5-a]pyridine, [1,2,4]triazolo[4,3-a]pyridine), imidazopyridine (for example, imidazo[1,5-a]pyridine), imidazopyrazine (for example, imidazo[1,2-a]pyrazine), imidazopyrimidine (for example, imidazo[1,2-a]pyrimidine), imidazopyridazine (for example, imidazo[1,2-b]pyridazine), naphthyridine (for example, 1,5-naphthyridine, 1,8-naphthyridine), quinoxaline, dihydroquinoxaline (for example, 1,2-dihydroquinoxaline), tetrahydroquinoxaline (for example, 1,2,3,4-tetrahydroquinoxaline), quinazoline, quinazoline-4 (3H)-one, dihydroquinazoline (for example, 2,3-dihydroquinazoline), pyrazolopyridine (for example, pyrazolo[1,5-a]pyridine,

pyrazolo[3,4-b]pyridine), pyrrolopyridine (for example, pyrrolo[2,3-b]pyridine), pyrrolo[2,3-b]pyridine-2 (3H)-one, and pyrazolopyrimidine (for example, pyrazolo[1,5-a]pyrimidine).

(15) Specific examples of an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 to 3 oxygen atoms alone as ring-constituting heteroatom in the above (c) and its oxide and dioxide, and the heterocycle in which a part or all of unsaturated bonds in its rings are reduced with hydrogen may include benzodioxole (for example, benzo[d][1,3]dioxole, benzo[c][1,2]dioxole).

(16) Specific examples of an unsaturated 3- to 8-membered monocyclic heterocycle containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom in the above (d) and its oxide and dioxide, and the heterocycle in which a part or all of unsaturated bonds in its ring are reduced with hydrogen may include oxazepine (for example, 1,2-oxazepine, 1,3-oxazepine, 1,4-oxazepine), dihydrooxazepine, tetrahydrooxazepine, oxazepan (for example, 1,2-oxazepan, 1,3-oxazepan, 1,4-oxazepan), 1,4-oxazepan-2-one, oxazine (for example, 1,4-oxazine), dihydrooxazine (3,4-dihydro-2H-1,4-oxazepine), morpholine, and morpholin-3-one.

(17) Specific examples of an unsaturated 7- to 12-membered bicyclic heterocycle containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms as ring-constituting heteroatom in the above (e) and its oxide and dioxide, and the heterocycle in which a part or all of unsaturated bonds in its rings are reduced with hydrogen may include benzothiazole (for example, benzo[d]thiazole).

(18) Specific examples of an unsaturated 3- to 8-membered monocyclic hydrocarbon ring in the above (f) and its oxide and dioxide, and the heterocycle in which a part or all of unsaturated bonds in its ring are reduced with hydrogen may include benzene, cyclohexene, and cyclohexane.

(19) When ring B is pyrimidine, preferably, ring C is selected from the group consisting of the following unsaturated rings and their oxides and dioxides (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrimidine, indole, pyrrolopyridine, indazole, benzimidazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, triazolopyridine, pyrazolopyrimidine, imidazopyrimidine, triazolopyrimidine, quinoline, isoquinoline, naphthyridine, quinazoline, quinoxaline, benzodioxole, oxazine, oxazepine, benzothiazole, and benzene.

(20) Regarding ring C in Compound [I] of the present invention, when ring B is benzene, naphthalene, pyridine, pyrazole or pyridazine, ring C is pyrimidine-2,4-dione or dihydropyrimidine-2,4-dione. Preferably, ring B is benzene or pyridine. R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —CN or —SF.sub.5, and preferably is halogen, C.sub.1-6 alkyl optionally substituted with halogen or —O—C.sub.1-6 alkyl optionally substituted with halogen, and more preferably is fluorine, methyl, trifluoromethyl, or —O-trifluoromethyl. R.sup.2 is halogen, C.sub.1-6 alkyl or —O—C.sub.1-6 alkyl, and preferably is fluorine, methyl or —O—methyl. R.sup.3 is halogen, C.sub.1-6 alkyl optionally substituted with halogen or C.sub.1-6 alkyl-O—, —O—C.sub.1-6 alkyl optionally substituted with halogen, —C.sub.1-6 alkyl-OH, —OH, —CN, —CONH.sub.2 or —NH.sub.2, preferably is C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl, —OH, —CONH.sub.2 or —NH.sub.2, and most preferably methyl, trifluoromethyl, —O-methyl, —OH, —CONH.sub.2 or —NH.sub.2. L is bond, C.sub.1-6 alkylene, —O— or —S—, preferably is bond or —O—, and most preferably —O—. k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent. 0 or 1 is preferable, and 0 is more preferable. m is 0, 1 or 2, and when m is 2, each R.sup.2 independently represents the same or different substituent. 0 or 1 is preferable, and 0 is more preferable. n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent. 0 or 1 is preferable.

(21) Presentation of options relating to the above substituents and preferable aspects of Compound [I] of the present invention include all combinations thereof as long as they are combinations with no contradiction.

(22) Preferable aspects of Compound [I] of the present invention are shown below. (1-1) In

Formula I, D is

(23) ##STR00014## ring A is benzene or pyridine; ring B is pyrimidine; ring C is selected from the group consisting of the following unsaturated rings and their oxides and dioxides (provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded), and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrimidine, indole, pyrrolopyridine, indazole, benzimidazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, triazolopyridine, pyrazolopyrimidine, imidazopyrimidine, triazolopyrimidine, quinoline, isoquinoline, naphthyridine, quinazoline, quinoxaline, benzodioxole, oxazine, oxazepine, benzothiazole, and benzene; R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen or —CN; R.sup.2 is —O—C.sub.1-6 alkyl; R.sup.3 is halogen, C.sub.1-6 alkyl optionally substituted with halogen or —O—C.sub.1-6 alkyl, —O—C.sub.1-6 alkyl optionally substituted with halogen, —C.sub.1-6 alkyl-OH, —OH, —CN, —CONH.sub.2 or —NH.sub.2; L is —O—; k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0 or 1; and n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent.

(24) (1-2) In Formula I, ring C is selected from the group consisting of the following unsaturated rings and their oxides, and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrrolopyridine, indazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, pyrazolopyrimidine, triazolopyrimidine, quinoline, isoquinoline, naphthyridine, quinoxaline, and benzene; R.sup.1 is halogen or C.sub.1-6 alkyl optionally substituted with halogen; R.sup.3 is C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —OH, —CONH.sub.2 or —NH.sub.2; L is —O—; k and n are 0 or 1; and m is 0.

(25) (1-3) In Formula I, ring C is selected from the group consisting of the following unsaturated rings and their oxides, and those in which a part or all of unsaturated bonds in these rings are reduced with hydrogen: pyridine, pyridazine, pyrazolopyridine, and Imidazopyridine; R.sup.3 is —OH or —NH.sub.2; L is —O—; k and m are 0; and n is 0 or 1.

(26) (1-4) A compound selected from the group consisting of the following compounds:

(27) ##STR00015## ##STR00016## ##STR00017## ##STR00018## ##STR00019## ##STR00020## or a salt thereof.

(28) (1-5) A compound selected from the group consisting of the following compounds:

(29) ##STR00021## ##STR00022## or a salt thereof.

(30) Other preferable aspects of Compound [I] of the present invention are shown below. (2-1) In Formula I, D is

(31) ##STR00023## or C.sub.1-6 alkyl optionally substituted with halogen; ring A is benzene or pyridine; ring B is pyridazine, pyridine, pyrazole, benzene, or naphthalene; ring C is pyrimidine-2,4-dione or dihydropyrimidine-2,4-dione; R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —CN or —SF.sub.5; R.sup.2 is halogen, C.sub.1-6 alkyl, or —O—C.sub.1-6 alkyl; R.sup.3 is C.sub.1-6 alkyl; L is bond, C.sub.1-6 alkylene, —O— or —S—; k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0, 1 or 2, and when m is 2, each R.sup.2 independently represents the same or different substituent; and n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent.

(32) (2-2) In Formula I, ring A is benzene; ring B is benzene, pyridine, or pyridazine; ring C is dihydropyrimidine-2,4-dione; R.sup.1 is halogen; L is —O—; k is 0 or 1; and m and n are 0.

(33) (2-3) A compound selected from the group consisting of the following compounds:

(34) ##STR00024## or a salt thereof.

(35) (2-4) A compound:

(36) ##STR00025## or a salt thereof.

(37) In this specification, the options and preferred embodiments for the different features of the compound, method and composition of the present invention as presented include all possible combinations of the options and preferred embodiments for these different features as long as they are consistent combinations.

(38) Methods for manufacturing the compound [I] of the present invention are explained below. The compound [I] of the present invention can be manufactured based on the manufacturing methods described below for example. The manufacturing methods described below are examples, and the method for manufacturing the compound [I] is not limited thereby.

(39) In the reaction formulae below, when performing an alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, amidation reaction etherification reaction, nucleophilic substitution reaction, addition reaction, oxidation reaction, reduction reaction or the like, these reactions are themselves performed by known methods. Examples of such methods include the methods described in Experimental Chemistry (Fifth Edition, edited by The Chemical Society of Japan, Maruzen Co., Ltd.); Organic Functional Group Preparations Second Edition, Academic Press, Inc., 1989; Comprehensive Organic Transformations, VCH Publishers, Inc., 1989; and P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis (Fourth Edition, 2006) and the like.

(40) ##STR00026## wherein Y and Y' represent a leaving group, and the other symbols have the same definitions as above.

(41) According to the reaction represented by Reaction Formula 1-1, Compound [I] of the present invention can be produced. Specifically, cyclic pinacol ester ((BPin).sub.2) of boronic acid can be added to Compound [IIa] to obtain Compound [IIa'], and then Compound [IIa'] can be bonded to Compound [IIIa] by Suzuki cross coupling to produce Compound [I].

(42) Examples of the "leaving group" used in the reaction above include halogen, C.sub.1-18 alkanesulfonyl, C.sub.1-8 alkanesulfonyloxy, arylsulfonyloxy, aralkylsulfonyloxy, trihalomethanesulfonyloxy, sulfonio, toluenesulfoxy and the like. Examples of preferred leaving group in the reaction include halogen.

(43) The "halogen" is fluorine, chlorine, bromine or iodine.

(44) Examples of the "C.sub.1-18 alkanesulfonyl" include C.sub.1-18 linear or branched alkanesulfonyl, and specific examples include methanesulfonyl, 1-propanesulfonyl, 2-propanesulfonyl, butanesulfonyl, cyclohexanesulfonyl, dodecanesulfonyl, octadecanesulfonyl and the like.

(45) Examples of the "lower alkanesulfonyloxy" include C.sub.1-6 linear or branched alkanesulfonyloxy, and specific examples include methanesulfonyloxy, ethanesulfonyloxy, 1-propanesulfonyloxy, 2-propanesulfonyloxy, 1-buthanesulfonyloxy, 3-buthanesulfonyloxy, 1-pentanesulfonyloxy, 1-hexanesulfonyloxy and the like.

(46) Examples of the "arenesulfonyloxy" include naphthalenesulfonyloxy and benzenesulfonyloxy, which may have 1 to 3 substituents selected from the group consisting of halogen, nitro, C.sub.1-6 linear or branched alkoxy and C.sub.1-6 linear or branched alkyl groups on the phenyl ring. Specific examples of these "benzenesulfonyloxy which may have substituents" include benzenesulfonyloxy, 4-methylbenzenesulfonyloxy, 2-methylbenzenesulfonyloxy, 4-nitrobenzenesulfonyloxy, 4-methoxybenzenesulfonyloxy, 2-nitrobenzenesulfonyloxy, 3-chlorobenzenesulfonyloxy and the like. Specific examples of "naphthalenesulfonyloxy" include  $\alpha$ -naphthalenesulfonyloxy,  $\beta$ -naphthalenesulfonyloxy and the like.

(47) Examples of the "aralkanesulfonyloxy" include naphthyl-substituted C.sub.1-6 linear or branched alkanesulfonyloxy and phenyl-substituted C.sub.1-6 linear or branched alkanesulfonyloxy which may have 1 to 3 substituents selected from the group consisting of halogen, nitro, C.sub.1-6 linear or branched alkoxy and C.sub.1-6 linear or branched alkyl on the phenyl ring. Specific examples of these "phenyl-substituted alkanesulfonyloxy" include phenylmethanesulfonyloxy, 2-phenylethanesulfonyloxy, 4-phenylbutanesulfonyloxy, 4-tolylmethanesulfonyloxy, 2-

tolylmethanesulfonyloxy, (4-nitrophenyl) methanesulfonyloxy, (4-methoxyphenyl) methanesulfonyloxy, (3-chlorophenyl) methanesulfonyloxy and the like. Examples of “naphthyl-substituted alkanesulfonyloxy” include  $\alpha$ -naphthylmethanesulfonyloxy,  $\beta$ -naphthylmethanesulfonyloxy and the like.

(48) A specific example of “trihaloalkanesulfonyloxy” group is trifluoromethanesulfonyloxy.

(49) Specific examples of the “sulfonio” include dimethylsulfonio, diethylsulfonio, dipropylsulfonio, di(2-cyanoethyl) sulfonio, di(2-nitroethyl) sulfonio, di-(aminoethyl) sulfonio, di(2-methylaminoethyl) sulfonio, di-(2-dimethylaminoethyl) sulfonio, di-(2-hydroxyethyl) sulfonio, di-(3-hydroxypropyl) sulfonio, di-(2-methoxyethyl) sulfonio, di-(2-carbamoylethyl) sulfonio, di-(2-carboxyethyl) sulfonio, di-(2-methoxycarbonylethyl) sulfonio, diphenylsulfonio and the like.

(50) The “palladium compound” to be used in the present reaction is not particularly limited, and examples thereof include tetravalent palladium catalysts such as sodium hexachloropalladium (IV) acid tetrahydrate and potassium hexachloropalladium (IV) acid; divalent palladium catalysts such as [1,1'-bis(diphenylphosphino) ferrocene]palladium (II) dichloride dichloromethane adduct (Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate (XPhos Pd G3), palladium (II) chloride, palladium (II) bromide, palladium (II) acetate, palladium (II) acetylacetonate, dichlorobis(benzonitrile) palladium (II), dichlorobis(acetonitrile) palladium (II), dichlorobis(triphenylphosphine) palladium (II), dichlorotetraammine palladium (II) and dichloro(cycloocta-1,5-diene) palladium (II), palladium (II) trifluoroacetate; and zerovalent palladium catalysts such as tris(dibenzylideneacetone) dipalladium (0) (Pd.sub.2 (dba).sub.3), tris(dibenzylideneacetone) dipalladium (0)-chloroform complex, and tetrakis(triphenylphosphine) palladium (0) (Pd(PPh.sub.3).sub.4). These palladium compounds are used alone or as a mixture of two or more of them.

(51) In the present reaction, the amount of the palladium compound used is not particularly limited and is usually in the range of 0.000001 to 20 mol in terms of palladium with respect of 1 mol of compound [IIa]. More preferably, the amount of the palladium compound used is in the range of 0.0001 to 5 mol in terms of palladium with respect of 1 mol of compound [IIa].

(52) Examples of the “base” to be used in the present reaction include an inorganic base, an organic base, and the like. Examples of the “inorganic base” include an alkali metal hydroxide (e.g., sodium hydroxide and potassium hydroxide), an alkaline earth metal hydroxide (e.g., magnesium hydroxide and calcium hydroxide), an alkali metal carbonate (e.g., sodium carbonate and potassium carbonate), an alkaline earth metal carbonate (e.g., magnesium carbonate and calcium carbonate), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate and potassium hydrogen carbonate), an alkali metal phosphate (e.g., sodium phosphate and potassium phosphate), an alkaline earth metal phosphate (e.g., sodium phosphate and potassium phosphate). Examples of the “organic bases” include trialkylamines (e.g., trimethylamine, triethylamine, and diisopropylethylamine), dialkylamines (e.g., diethylamine, diisopropylamine), picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These bases are used alone or as a mixture of two or more of them.

(53) Regarding “boronic acid” or “boronic acid ester” used in this reaction, those separately produced, isolated and purified may be used. For example, bispinacol diborane may be reacted with a halogenated compound of a precursor and the like in the presence of a palladium compound, and the reaction product may be used for Suzuki cross coupling without isolation and purification.

(54) The “solvent” used in this reaction may be any solvent that is inactive in the reaction, and examples thereof include water, ethers (such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether or ethylene glycol dimethyl ether), hydrocarbons (such as hexane), halohydrocarbons (such as methylene chloride, chloroform, 1,2-dichloroethane or carbon tetrachloride), aromatic hydrocarbons (such as benzene, toluene or

xylene), lower alcohols (such as methanol, ethanol or isopropanol), polar solvents (such as N,N-dimethylformamide (DMF), N-methylpyrrolidine (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric acid triamide or acetonitrile), ketons (such as acetone or methylethylketone), esters (such as methyl acetate or ethyl acetate). One of these solvents alone or a mixture of two or more kinds may be used.

(55) Other reaction conditions (a reaction temperature, a reaction time, etc.) can be appropriately determined based on a known Suzuki cross coupling reaction.

(56) ##STR00027## wherein Y is a leaving group, and the other symbols have the same definitions as above.

(57) According to the reaction represented by Reaction Formula 1-2, Compound [I] of the present invention can be produced. Specifically, Compound [IIa] can be bonded to Compound [IIIb] by Suzuki cross coupling to produce Compound [I].

(58) The palladium compound, base, solvent, and the like that can be used in Reaction Formula 1-2 are the same as those that can be used in Reaction Formula 1-1.

(59) ##STR00028## wherein Y is a leaving group, and the other symbols have the same definitions as above.

(60) Compound [I] of the present invention can be produced according to the reaction represented by Reaction Formula 1-3. Specifically, Compound [IIa] can be bonded to Compound [IIIc] by Suzuki cross coupling to produce Compound [I].

(61) The palladium compound, base, solvent, and the like that can be used in Reaction Formula 1-3 are the same as those that can be used in Reaction Formula 1-1.

(62) ##STR00029## wherein symbols have the same definitions as above.

(63) According to the reaction represented by Reaction Formula 2-1, Compound [Ia] included in Compound [I] of the present invention can be produced. Specifically, Compound [VI] is added to an amino group of Compound [IIb], and chlorine of the product is then released for cyclization, and thus Compound [Ia] can be produced.

(64) Examples of “base” used in this reaction include inorganic bases and organic bases. Examples of “inorganic base” include alkali metal hydroxides (for example, sodium hydroxide, potassium hydroxide), alkali metal carbonates (for example, sodium carbonate, potassium carbonate), alkali metal bicarbonates (for example, sodium bicarbonate, potassium bicarbonate), sodium hydride (NaH), and sodium hexamethyldisilazide (NaHMDS). Examples of “organic base” include trialkylamines (for example, trimethylamine, triethylamine), Huenig's base (N,N-diisopropylethylamine), pyridine, and N-methylmorpholine.

(65) The “solvent” used in this reaction may be any solvent that is inactive in the reaction, and examples thereof include water, ethers (such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether or ethylene glycol dimethyl ether), hydrocarbons (such as hexane), halohydrocarbons (such as methylene chloride, chloroform, 1,2-dichloroethane or carbon tetrachloride), aromatic hydrocarbons (such as benzene, toluene or xylene), lower alcohols (such as methanol, ethanol or isopropanol), polar solvents (such as N,N-dimethylformamide (DMF), N-methylpyrrolidine (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric acid triamide or acetonitrile), ketons (such as acetone or methylethylketone), esters (such as methyl acetate or ethyl acetate). One of these solvents alone or a mixture of two or more kinds may be used.

(66) Other reaction conditions (reaction temperature, reaction time, etc.) can be appropriately determined based on a generally known condensation reaction. For example, the reaction temperature may be from room temperature to a heating reflux temperature of a solvent, and the reaction time may be from 10 minutes to 10 hours.

(67) ##STR00030## wherein symbols have the same definitions as above.

(68) According to the reaction represented by Reaction Formula 2-2, Compound [Ib] included in Compound [I] of the present invention can be produced. Specifically, Compound [III](acrylic acid)



is 1,4-added to an amino group of Compound [IIb] and next, an amino group of the product is converted into a urea derivative using urea and cyclized (intramolecular amidation), and thus Compound [Ib] can be produced.

(69) The “solvent” used in this reaction may be any solvent that is inactive in the reaction, and examples thereof include water, ethers (such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether or ethylene glycol dimethyl ether), hydrocarbons (such as hexane), halohydrocarbons (such as methylene chloride, chloroform, 1,2-dichloroethane or carbon tetrachloride), aromatic hydrocarbons (such as benzene, toluene or xylene), lower alcohols (such as methanol, ethanol or isopropanol), polar solvents (such as N,N-dimethylformamide (DMF), N-methylpyrrolidine (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric acid triamide or acetonitrile), ketons (such as acetone or methylethylketone), esters (such as methyl acetate or ethyl acetate). One of these solvents alone or a mixture of two or more kinds may be used.

(70) Examples of “acid” used in the reaction include inorganic acids and organic acids. Examples of “inorganic acid” include hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, and phosphoric acid. Examples of “organic acid” include acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, and 10-camphorsulfonic acid.

(71) Other reaction conditions (reaction temperature, reaction time, etc.) can be appropriately determined based on a generally known 1,4-addition reaction, and amidation reaction.

(72) ##STR00031## wherein Y is a leaving group, Li is —O—, —S—, or C.sub.1-6 alkylene, and the other symbols have the same definitions as above.

(73) According to the reaction represented by Reaction Formula 3-1, Compound [Ic] included in Compound [I] of the present invention can be produced. Specifically, Compound [Ic] can be produced by releasing a leaving group Y of Compound [V] and substituting with Compound [IV].

(74) Examples of “base” used in this reaction include inorganic bases. Examples of “inorganic base” include alkali metal hydroxides (for example, sodium hydroxide, potassium hydroxide), alkali metal carbonates (for example, sodium carbonate, potassium carbonate), alkali metal bicarbonates (for example, sodium bicarbonate, potassium bicarbonate), sodium hydride (NaH), and sodium hexamethyldisilazide (NaHMDS). Examples of “organic base” include trialkylamines (for example, trimethylamine, triethylamine), Huenig's base (N,N-diisopropylethylamine), pyridine, and N-methylmorpholine.

(75) The “solvent” used in this reaction may be any solvent that is inactive in the reaction, and examples thereof include water, ethers (such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether or ethylene glycol dimethyl ether), hydrocarbons (such as hexane), halohydrocarbons (such as methylene chloride, chloroform, 1,2-dichloroethane or carbon tetrachloride), aromatic hydrocarbons (such as benzene, toluene or xylene), lower alcohols (such as methanol, ethanol or isopropanol), polar solvents (such as N,N-dimethylformamide (DMF), N-methylpyrrolidine (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric acid triamide or acetonitrile), ketons (such as acetone or methylethylketone), esters (such as methyl acetate or ethyl acetate). One of these solvents alone or a mixture of two or more kinds may be used.

(76) Other reaction conditions (a reaction temperature, a reaction time, etc.) can be appropriately determined based on a generally known condensation reaction. For example, the reaction temperature may be from room temperature to 100° C., and the reaction time may be 1 hour to 10 hours.

(77) In each of the reactions in the above reaction formulae, the reaction product can be used in the next reaction either as is in the form of the reaction solution or as a crude product, but it can also be isolated from the reaction mixture by normal methods and easily purified by normal separation techniques. Examples of normal separation techniques include recrystallization, distillation and

chromatography.

(78) The starting raw material compounds, intermediate compounds and object compounds in each of the above steps and the compound [I] of the present invention itself all include geometric isomers, stereoisomers, optical isomers and tautomers. The respective isomers can be separated by ordinary optical resolution methods. They can also be manufactured from raw material compounds having suitable optical activity.

(79) The compound [I] of the present invention can be manufactured by the synthesis methods shown in the reaction formulae above, or by analogous methods.

(80) Unless specific production methods are specified, the raw material compounds used in the manufacture of the compound [I] of the present invention may be commercial compounds, or may be produced by known methods or analogous methods.

(81) The starting raw material compounds and object compounds in each step above may be used in the form of appropriate salts. Examples of such salts include salts similar to those given as examples of salts of compound [I] of the present invention below.

(82) When the compounds obtained in each step or commercial products are free compounds, they can be converted to the object salts by known methods. When the compounds obtained in each step or commercial products are salts, they can be converted to free form or into other object salts by known methods.

(83) The compound [I] of the present invention also includes embodiments that are pharmaceutically acceptable salts, and in some cases the compounds may also form an acid addition salt or a salt with a base depending on the kinds of substituents. Examples of the “acid” here include inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid; and organic acids such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and the like.

Examples of the “base” include inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate; organic bases such as methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline and choline; and ammonium salts and the like. The compound may also form a salt with an amino acid such as lysine, arginine, aspartic acid, glutamic acid or the like.

(84) The present invention also encompasses various hydrates, solvates and crystal polymorphisms of the compound [I] and salts thereof.

(85) The compound [I] of the present invention also includes compounds in which one or more isotope atoms have been substituted for one or more atoms. Examples of isotope atoms include deuterium (2H), tritium (3H), 13C, 15N, 18O and the like.

(86) The compound [I] of the present invention includes pharmaceutically acceptable prodrugs. Examples of substituents that can be modified to make prodrugs include reactive functional groups such as —OH, —COOH, amino and the like. The modifying groups of these functional groups are selected appropriately from the “substituents” in this specification.

(87) The compound [I] or a salt thereof of the present invention may be in the form of a pharmaceutically acceptable co-crystal or co-crystal salts. A co-crystal or co-crystal salt here means a crystalline substance composed at room temperature of two or more independent solids each having different physical properties (such as structure, melting point, heat of fusion and the like). Co-crystals and co-crystal salts can be manufactured appropriately by well-known co-crystallization methods.

(88) The compound [I] and a salt thereof of the present invention have excellent effects in the treatment, prevention and/or diagnosis of seizure in disease involving epileptic seizure or convulsive seizure. The term epileptic seizure is applicable to any of the seizure types classified below: focal onset seizure (also called partial seizure) with motor onset (including automatism,

atonic seizure, clonic seizure, epileptic spasms, hyperkinetic seizure, myoclonic seizure and tonic seizure) and non-motor onset (including autonomic seizure, behavior arrest seizure, cognitive seizure, emotional seizure and sensory seizure), and focal to bilateral tonic-clonic seizure (secondary generalization of partial seizure); generalized onset seizure including motor seizure (including tonic-clonic seizure, clonic seizure, tonic seizure, myoclonic seizure, myoclonic-tonic-clonic seizure, myoclonic-atonic seizure, atonic seizure and epileptic spasms) and non-motor seizure (including typical absence seizure, atypical absence seizure, myoclonic absence seizure and eyelid myoclonic seizure); and seizures of unknown onset including motor seizure (including tonic-clonic seizure and epileptic spasms) and non-motor seizure (including behavior arrest seizure).

(89) Examples of the disease involving epileptic seizure or convulsive seizure include Dravet syndrome, Lennox-Gastaut syndrome, West syndrome (*epilepsia nutans*), Ohtahara syndrome, Doose syndrome, Landau-Kleffner syndrome, Rasmussen syndrome, Aicardi syndrome, Panayiotopoulos syndrome, Kojewnikow syndrome, Tassinari syndrome, Geschwind syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, mesial temporal lobe epilepsy, epilepsy with structural/metabolic cause (epilepsy after stroke, traumatic epilepsy, infectious epilepsy, epilepsy associated with cerebrovascular disorder, epilepsy associated with brain tumor, epilepsy associated with neurodegenerative disease, epilepsy associated with autoimmune disorder, etc.), and congenital malformation, congenital metabolic abnormality (for example, phenylketonuria, mitochondrial disease, lysosomal disease, Sturge-Weber syndrome, etc.) and congenital genetic abnormality (Rett's syndrome, Angelman's syndrome, 5p syndrome, 4p syndrome, Down's syndrome, etc.).

(90) The compound [I] or a salt thereof of the present invention is also effective in the treatment, prevention and/or diagnosis of multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus. In the present invention, multiple drug resistant seizure and refractory seizure are defined as seizure that cannot be controlled because one or two or more antiepileptic drugs are ineffective or insufficiently effective or the like, regardless of the type of epileptic seizure as described above.

(91) Moreover, the compound [I] and a salt thereof of the present invention have excellent features for use as active ingredients in pharmaceuticals, and for example have excellent features such as few side effects, tolerability, stability (storage stability, metabolic stability, etc.) and the like. These groups of compounds of the present invention also have effects as preventative and/or therapeutic agents against refractory epileptic seizure in which conventional drug therapy is not successful.

(92) Next, a medical preparation (hereunder also called a “pharmaceutical composition”) containing a compound [I] or a salt thereof of the present invention as an active ingredient is explained.

(93) The medical preparation is obtained by formulating a compound [I] or a salt thereof of the present invention in the form of an ordinary medical preparation, and is prepared using a compound [I] or a salt thereof of the present invention and a pharmaceutically acceptable carrier. Examples of the carrier include commonly used diluents or excipients such as fillers, bulking agents, binders, humectants, disintegrants, surfactants, lubricants and the like.

(94) Such a medical preparation can be selected from various forms according to the therapeutic objective, and examples thereof include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, injections (liquids, suspensions, etc.) and the like.

(95) A wide range of known carriers may be used when molding the preparation in the form of a tablet, and examples thereof include excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbants such as colloidal silicic acid; and lubricants such as magnesium stearate, polyethylene glycol and the like.

(96) Moreover, the tablet may as necessary be made into a tablet with an ordinary coating, such as for example a sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet,

double tablet or multilayer tablet.

(97) A wide range of known carriers may be used when molding the preparation in the form of a pill, and examples thereof include excipients such as glucose; binders such as gum arabic powder; and disintegrants such as laminaran and the like . . .

(98) A wide range of known diluents may be used when forming the preparation as a liquid, emulsion or suspension, and examples thereof include water and the like. Ordinary solubilizing agents and buffers may also be included, as well as colorants, preservatives, aromatics, flavorings, sweeteners and other drugs and the like as necessary.

(99) A wide range of known carriers may be used when forming the preparation as a suppository, and examples thereof include cocoa butter and the like.

(100) When the preparation is an injection, the liquid, emulsion or suspension is preferably sterilized, and is also preferably isotonic with blood. An amount of sodium chloride sufficient to prepare an isotonic injection may be included in the injection, and another drug, soothing agent or the like may also be included.

(101) The amount of the compound [I] or a salt thereof that is contained in the medical preparation is not particularly limited and may be selected appropriately from a wide range, but normally the compound [I] or a salt thereof of the present invention is preferably contained in the amount of 1% to 70% of the medical preparation.

(102) The method for administering the medical preparation of the present invention is not particularly limited, and it can be administered by a method suited to the dosage form, the age and sex of the patient, the disease status and other conditions. For example, it can be administered orally if it is in the form of a tablet, pill, liquid, suspension, emulsion, granules or capsules. If it is an injection, it can be administered intravenously either alone or in a mixture with an ordinary replacement fluid such as glucose or amino acids, or else it can be administered by itself intramuscularly, intradermally, subcutaneously or intraperitoneally as necessary. In the case of a suppository, it can be administered in the rectum.

(103) The dose of the medical preparation may be selected according to the administration method, the age and sex of the patient, the severity of the disease and other conditions, but normally 0.01 to 100 mg or preferably 0.1 to 50 mg per 1 kg of body weight can be administered per day in one or more administrations.

(104) This dose is affected by various conditions, and in some cases a dose below the aforementioned range may be sufficient, while in others a dose above the aforementioned range may be necessary.

(105) The compound [I] or a salt thereof of the present invention can be used in combination with various treatment or preventative agents for disease for which the compound [I] is thought to be effective. Such combined use may be by simultaneous administration, or else by separate administration, either continuously or with a suitable interval in between. Preparations that are administered simultaneously may be formulated separately or combination.

(106) A pharmaceutical composition containing the compound [I] or a salt thereof of the present invention together with a pharmaceutically acceptable carrier and/or excipient is provided by one embodiment of the present invention.

(107) Another embodiment provides a therapeutic, preventative and/or diagnostic agent for seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), containing the compound [I] or a salt thereof of the present invention together with a pharmaceutically acceptable carrier and/or excipient.

(108) Yet another embodiment provides a therapeutic, preventative and/or diagnostic pharmaceutical composition for seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), containing the compound [I] or a salt thereof of the present

invention together with a pharmaceutically acceptable carrier and/or excipient.

(109) Yet another embodiment provides a method for treating, preventing and/or diagnosing seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus), which comprises administering to a human in need thereof an effective amount of the compound [I] or a salt thereof of the present invention.

(110) Yet another embodiment provides the compound [I] or a salt thereof of the present invention for use in the treatment, prevention and/or diagnosis of seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus).

(111) Yet another embodiment provides the use of the compound [I] or a salt thereof of the present invention in the manufacture of a drug for treating, preventing and/or diagnosing seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus).

## EXAMPLES

(112) The present invention is explained in further detail below through the following Test Examples, Reference Examples and Examples, but these do not limit the present invention, and these may be changed to the extent that they do not deviate from the scope of the present invention.

(113) The following abbreviations are used in this Description.

(114) TABLE-US-00001 Abbreviations Words DBU 1,8-diazabicyclo [5.4.0]-7-undecene DCC dicyclohexylcarbodiimide DCE 1,2-dichloroethane DCM dichloromethane DEAD diethylazodicarboxylate DHP 3,4-dihydro-2H-pyran DIBAL diisobutylaluminum hydride DIBOC di-*t*-butyl dicarbonate DIPEA diisopropylethylamine DMA N,N-dimethylacetamide DMAP 4-(dimethylamino) pyridine DME dimethoxyethane DMF N,N-dimethylformamide DMSO dimethyl sulfoxide DPPA diphenylphosphoryl azide Et.sub.2O diethyl ether EtOH ethanol HCl hydrochloric acid Hexane n-hexane HOBt 1-hydroxybenzotriazole IPA 2-propanol IPE diisopropyl ether K.sub.2CO.sub.3 potassium carbonate K.sub.3PO.sub.4 tripotassium phosphate KHCO.sub.3 potassium bicarbonate KOH potassium hydroxide KOtBu potassium *t*-butoxide LAH lithium aluminum hydride LDA lithium diisopropylamide LHMDs lithium hexamethyldisilazide LIOH lithium hydroxide MeCN acetonitrile MEK 2-butanone MeOH methanol NaBH.sub.4 sodium borohydride Na.sub.2CO.sub.3 sodium carbonate NaH sodium hydride NaHCO.sub.3 sodium hydrogen carbonate NaOH sodium hydroxide NaOtBu sodium *t*-butoxide NBS N-bromosuccinimide NCS N-chlorosuccinimide NMP N-methylpyrrolidone Pd.sub.2 (dba) = tris (dibenzylideneacetone) dipalladium (0) PdCl.sub.2 (dppf) [1,1'- DCM bis (diphenylphosphino) ferrocene] palladium (II) dichloride dichloromethane adduct Pd (OAc).sub.2 palladium (II) acetate Pd (PPh.sub.3).sub.4 tetrakis (triphenylphosphine) palladium (0) Pd/C palladium-carrying carbon Pt/C platinum-carrying carbon PEG polyethylene glycol PPTS pyridinium *p*-toluenesulfonate TBAF tetra-*n*-butylammonium fluoride TCDI 1,1'-thiocarbonyldiimidazole TEA triethylamine TFA trifluoroacetic acid THE tetrahydrofuran TPP triphenylphosphine WSC 3-ethyl-1-(3-dimethylaminopropyl) carbodiimide ZCl benzyl chloroformate XPhos Pd G3 (2-dicyclohexylphosphino-2',4',6' - triisopropyl-1,1'-biphenyl) [2-(2'-amino-1,1'- biphenyl)]palladium (II) methanesulfonate

(115) In the examples below, "room temperature" normally indicates from about 10° C. to about 35° C. The ratios indicated for mixed solvents are volume ratios unless otherwise specified.

Percentages indicate weight % unless otherwise specified.

(116) The <sup>1</sup>H NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform type NMR (either of Bruker AVANCE III 400 (400 MHz) and Bruker AVANCE III HD (500 MHz)).

(117) In silica gel column chromatography, when denoted as basic, aminopropylsilane-bonded silica gel was used.

(118) The absolute configuration of the compound was determined by known X-ray crystal structure analysis methods (for example, Shigeru Oba and Shigenobu Yano, "Basic Course for Chemists 12, X-ray Crystal Structure Analysis" (First Edition, 1999)), or estimated from empirical rules of Shi asymmetric epoxidation (Waldemar Adam, Rainer T. Fell, Chantu R. Saha-Moller and Cong-Gui Zhao: Tetrahedron: Asymmetry 1998, 9, 397-401. Yuanming Zhu, Yong Tu, Hongwu Yu, Yian Shi: Tetrahedron Lett. 1988, 29, 2437-2440).

## REFERENCE EXAMPLES

### Reference Example 1

#### Synthesis of 5-Bromo-2-Phenoxypyrimidine

(119) 5-Bromo-2-chloropyrimidine (25.0 g) was added to a suspension containing phenol (13.6 mL), K.sub.2CO.sub.3 (26.8 g), and DMF (250 mL), and the mixture was stirred at room temperature overnight. Water was added to the reaction solution, and the generated crystals were then collected by filtration and washed with water to obtain the object compound (27.7 g).

### Reference Example 2

#### Synthesis of 2-Phenoxy-5-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-Yl)Pyrimidine

(120) A mixture containing 5-bromo-2-phenoxypyrimidine (1.00 g), (BPin).sub.2 (1.315 g), PdCl.sub.2 (dppf) DCM (0.163 g), AcOK (0.782 g), and 1,4-dioxane (10 mL) was heated to reflux under a nitrogen atmosphere for 10 hours. Water and AcOEt were added to the reaction solution and the mixture was filtered through Celite. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate, and then concentrated. The residue was suspended in IPE, insoluble matter were filtered off, the filtrate was concentrated, and the obtained solid was washed with Hexane to obtain the object compound (646 mg).

### Reference Example 18

#### Synthesis of 3-Methoxy-6-(2-(Methylthio)Pyrimidin-5-Yl)Pyridazine

(121) A mixture containing 3-chloro-6-methoxypyridazine (206.3 mg), 2-(methylthio)pyrimidinyl-5-boronic acid pinacol ester (425.4 mg), K.sub.3PO.sub.4 (663.4 mg), PdCl.sub.2 (dppf) DCM (48.6 mg), 1,4-dioxane (20 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 1.5 hours. The reaction solution was concentrated, and the residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (242.6 mg).

### Reference Example 19

#### Synthesis of 3-Methoxy-6-(2-(Methylsulfonyl)Pyrimidin-5-Yl)Pyridazine

(122) A mixture containing 3-methoxy-6-(2-(methylthio)pyrimidin-5-yl)pyridazine (242.6 mg), water content 77% m-CPBA (627.9 mg), and DCM (20 mL) was stirred at 0° C. for 1 hour, and additionally stirred at room temperature overnight. The reaction solution was poured into ice and a saturated NaHCO.sub.3 aqueous solution, and the product was extracted with DCM. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (166.7 mg).

### Reference Example 21

#### Synthesis of 5-(2-(Methylthio)Pyrimidin-5-Yl)Pyridin-2-Amine

(123) A mixture containing 2-(methylthio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (1.96 g), 2-amino-5-bromopyridine (1.037 g), K.sub.3PO.sub.4 (3.86 g), PdCl.sub.2 (dppf) DCM (273.3 mg), 1,4-dioxane (30 mL), and water (3 mL) was heated to reflux under a nitrogen atmosphere for 6 hours. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel chromatography (Hexane/AcOEt) to obtain the object compound (1.175 g).

### Reference Example 22

#### Synthesis of 5-(2-(Methylsulfinyl)Pyrimidin-5-Yl)Pyridin-2-Amine

(124) A mixture containing 5-(2-(methylthio)pyrimidin-5-yl)pyridin-2-amine (1.175 g), Oxone (registered trademark) (2.43 g), THF (30 mL), and water (10 mL) was stirred under a nitrogen

atmosphere at 0° C. for 10 minutes and then stirred at room temperature for 2.75 hours. The reaction solution was poured into ice and a saturated NaHCO<sub>3</sub> aqueous solution, and the product was extracted with DCM. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (AcOEt, AcOEt/MeOH) to obtain the object compound (462 mg).

#### Reference Example 23

##### Synthesis of 5-Bromo-2-(Dodecylthio)Pyrimidine

(125) A mixture containing 5-bromo-2-chloropyrimidine (2.30 g), 1-dodecanethiol (3.2 mL), K<sub>2</sub>CO<sub>3</sub> (2.57 g), and DMF (20 mL) was stirred at room temperature overnight. Water was added thereto, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (3.56 g).

#### Reference Example 24

##### Synthesis of 5-(2-(Dodecylthio)Pyrimidin-5-Yl)Pyridin-2-Amine

(126) A mixture containing 5-bromo-2-(dodecylthio)pyrimidine (1.008 g), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (811.6 mg), K<sub>3</sub>PO<sub>4</sub> (1.82 g), PdCl<sub>2</sub>(dppf) DCM (107.7 mg), 1,4-dioxane (20 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 2.25 hours. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (1.01 g).

#### Reference Example 25

##### Synthesis of 5-(2-(Dodecylsulfinyl)Pyrimidin-5-Yl)Pyridin-2-Amine

(127) A mixture containing 5-(2-(dodecylthio)pyrimidin-5-yl)pyridin-2-amine (1.010 g), Oxone (registered trademark) (1.97 g), THF (40 mL), and water (10 mL) was stirred at 0° C. for 25 minutes, and then stirred at room temperature overnight. The reaction solution was poured into a solution mixture containing ice, a saturated NaHCO<sub>3</sub> aqueous solution, and DCM and extracted with DCM. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (163 mg).

#### Reference Example 26

##### Synthesis of 3-(Benzyloxy)-6-(2-Phenoxypyrimidin-5-Yl)Pyridazine

(128) A mixture containing 5-bromo-2-phenoxypyrimidine (2.96 g), (BPin)<sub>2</sub>PdCl<sub>2</sub> (3.68 g), PdCl<sub>2</sub>(dppf) DCM (0.370 g), AcOK (1.78 g), and 1,4-dioxane (20 mL) was heated to reflux under a nitrogen atmosphere for 3 hours. 3-(Benzyloxy)-6-chloropyridazine (2.00 g), PdCl<sub>2</sub>(dppf) DCM (0.370 g), K<sub>3</sub>PO<sub>4</sub> (3.85 g), and water (5 mL) were added to the reaction solution and heated to reflux for 2 hours. Water and AcOEt were added to the reaction solution and the mixture was filtered through Celite. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt), and the obtained solid was then washed with AcOEt to obtain the object compound (2.54 g).

#### Reference Example 35

##### Synthesis of 4-(2-Phenoxypyrimidin-5-Yl)-2-(Tetrahydro-2H-Pyran-2-Yl)Pyridazin-3 (2H)-One

(129) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (1.496 g), 4-bromo-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3 (2H)-one (1.00 g), PdCl<sub>2</sub>(dppf) DCM (0.063 g), K<sub>3</sub>PO<sub>4</sub> (1.229 g), 1,4-dioxane (10 mL), and water (3 mL) was stirred at 100° C. overnight. Water was added to the reaction solution and the product was extracted with AcOEt. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) and the obtained solid was then washed with EtOH to obtain the object compound (1.087 g).

#### Reference Example 38

##### Synthesis of 5-Bromo-1-Triisopropylsilyl-1H-Pyrazolo[3,4-b]Pyridine

(130) 60% NaH (0.933 g) was added to a DMF (20 mL) solution containing 5-bromo-1H-pyrazolo[3,4-b]pyridine (4.20 g) at 0° C. while stirring. After 20 minutes, chlorotriisopropylsilane (4.99 mL) was added thereto and the mixture was stirred for 30 minutes. The reaction solution was poured into ice water, and the precipitated solid was collected by filtration. The solid was dissolved in AcOEt and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (6.70 g).

#### Reference Example 39

##### Synthesis of 4-Methoxy-2-Phenoxy-5-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-Yl)Pyrimidine

(131) A solution mixture containing 5-bromo-4-methoxy-2-phenoxy pyrimidine (15.00 g), (BPin).sub.2 (14.9 g), AcOK (10.5 g), PdCl.sub.2 (dppf) DCM (2.18 g), and DMSO (60 mL) was stirred under a nitrogen atmosphere at 100° C. for 3 hours. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (9.61 g).

#### Reference Example 40

##### Synthesis of 2-(Dodecylthio)-5-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-Yl)Pyrimidine

(132) A mixture containing 5-bromo-2-(dodecylthio)pyrimidine (2.548 g), (BPin).sub.2 (2.17 g), AcOK (1.48 g), PdCl.sub.2 (dppf) DCM (280.1 mg), and DMSO (20 mL) was stirred under a nitrogen atmosphere at 100° C. for 2 hours. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (1.90 g).

#### Reference Example 41

##### Synthesis of 6-(2-(Dodecylthio)Pyrimidin-5-Yl) Imidazo[1,2-a]Pyridine

(133) A mixture containing 2-(dodecylthio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (3.00 g), 6-bromoimidazo (1,2-a)pyridine (1.53 g), PdCl.sub.2 (dppf) DCM (0.301 g), K.sub.3PO.sub.4 (3.13 g), 1,4-dioxane (20 mL), and water (10 mL) was stirred at 95° C. for 1 hour. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (2.05 g).

#### Reference Example 42

##### Synthesis of 6-(2-(Dodecylsulfonyl)Pyrimidin-5-Yl) Imidazo[1,2-a]Pyridine

(134) A mixture containing 6-(2-(dodecylthio)pyrimidin-5-yl) imidazo[1,2-a]pyridine (2.00 g), Oxone (registered trademark) (7.75 g), THF (40 mL), and water (20 mL) was stirred at room temperature for 5 hours. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (910 mg).

#### Reference Example 43

##### Synthesis of 5-Nitro-2-Phenoxy pyrimidine

(135) A mixture containing phenol (6.61 mL), potassium carbonate (12.99 g), 2-chloro-5-nitropyrimidine (10 g), and DMF (80 mL) was stirred at room temperature overnight. Water was added to the reaction solution and the generated crystals were collected by filtration and washed with water to obtain the object compound (6.55 g).

#### Reference Example 44

##### Synthesis of 2-Phenoxy pyrimidin-5-Amine



(136) 5-Nitro-2-phenoxyypyrimidine (7.45 g) and hydrous 10% Pd/C (3 g) were suspended in EtOH (100 mL) and stirred under a hydrogen atmosphere at room temperature for 4 hours. The reaction solution was filtered through Celite, the filtrate was concentrated, and the obtained solid was washed with IPE to obtain the object compound (4.73 g).

#### Reference Example 45

##### Synthesis of 1-(3-Chloropropyl)-3-(2-Phenoxyypyrimidin-5-Yl) Urea

(137) A THF (10 mL) solution containing 2-phenoxyypyrimidin-5-amine (1.00 g) was stirred at room temperature and 3-chloropropyl isocyanate (0.713 mL) was added thereto, and the mixture was stirred overnight. The precipitated solid was collected by filtration and washed with THE to obtain the object compound (756 mg).

#### Reference Example 46

##### Synthesis of 2-(3-Fluoromethoxyphenoxy)-5-Nitropyrimidine

(138) A mixture containing m-fluorophenol (5.45 mL), potassium carbonate (10.40 g), 2-chloro-5-nitropyrimidine (8.00 g), and DMF (80 mL) was stirred at room temperature overnight. Water was added to the residue, and the product was extracted with AcOEt. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate, and then concentrated to obtain the object compound (8.63 g).

#### Reference Example 47

##### Synthesis of 2-(3-Fluorophenoxy)Pyrimidin-5-Amine

(139) 2-(3-Fluoromethoxyphenoxy) nitropyrimidine (8.65 g) and 50% water-containing 10% Pd/C (3 g) were suspended in EtOH (100 mL) and stirred under a hydrogen atmosphere at room temperature for 16 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through medium pressure column chromatography (DCM/AcOEt), and the obtained solid was then washed with hexane to obtain the object compound (3.77 g).

#### Reference Example 50

##### Synthesis of 2-Phenoxy-5-(4-(Triisopropylsilyloxy) Piperidin-1-Yl)Pyrimidine

(140) A solution mixture containing 5-bromo-2-phenoxyypyrimidine (400 mg), 4-(triisopropylsilyloxy) piperidine (451 mg), Pd(OAc)<sub>2</sub> (17.9 mg), tBu<sub>3</sub>PMg.HBF<sub>4</sub> (23.1 mg), NaOtBu (153 mg) and toluene (6 mL) was stirred under a nitrogen atmosphere at 100° C. for 3 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (250 mg).

#### Reference Example 56

##### Synthesis of (R)-1-(2-Phenoxyypyrimidin-5-Yl)-4-(Triisopropylsilyloxy) Piperidin-2-One

(141) A solution mixture containing 5-iodo-2-phenoxyypyrimidine (500 mg), (R)-4-(triisopropylsilyloxy) piperidin-2-one (501 mg), copper iodide (I) (5.68 µl), trans-N,N'-dimethylcyclohexane-1,2-diamine (0.053 mL), K<sub>3</sub>PO<sub>4</sub> (712 mg), and 1,4-dioxane (6 mL) was stirred under a nitrogen atmosphere at 95° C. for 3 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (340 mg).

#### Reference Example 58

##### Synthesis of 1-Fluoro-3-(4-Nitrophenoxy)Benzene

(142) A mixture containing m-fluorophenol (41.7 g), 4-fluoronitrobenzene (50.0 g), K<sub>2</sub>CO<sub>3</sub> (63.7 g), and DMF (250 mL) was stirred at 80° C. for 6 hours. The reaction solution was poured into ice water, and precipitates were collected by filtration and washed with water to obtain the object compound (80.7 g).

#### Reference Example 59

##### Synthesis of 4-(3-Fluorophenoxy) Aniline

(143) Zinc powder (50.5 g) was added to a mixture containing 1-fluoro-3-(4-nitrophenoxy)benzene

(30 g), ammonium chloride (41.3 g), EtOH (225 mL), and water (75 mL) while stirring the mixture at room temperature, and additionally the mixture was stirred at 60° C. for 1 hour. The insoluble matter was filtered through Celite, the filtrate was concentrated, and the residue was then extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (26 g).

#### Reference Example 60

##### Synthesis of 1-(4-Bromophenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(144) A toluene (50 mL) solution containing 4-bromoaniline (7.66 g) and acrylic acid (3.05 mL) was stirred at 80° C. overnight. The reaction solution was concentrated, urea (5.35 g) and acetic acid (20 mL) were added thereto, and the mixture was heated to reflux for 3 hours. The precipitated solid was collected by filtration and washed with EtOH to obtain the object compound (5.44 g).

#### Reference Example 61

##### Synthesis of 1-(4-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-Yl)Phenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(145) A mixture containing 1-(4-bromophenyl)dihydropyrimidine-2,4 (1H,3H)-dione (2.78 g), (BPin).sub.2 (3.15 g), AcOK (3.04 g), PdCl.sub.2 (dppf) DCM (0.422 g), and DMSO (30 mL) was stirred under an argon atmosphere at 100° C. for 5 hours. The reaction solution was poured into ice water and extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/MeOH) to obtain the object compound (0.82 g).

#### Reference Example 76

##### Synthesis of 1-[4-(3-Hydroxyphenoxy)Phenyl]Dihydropyrimidine-2,4 (1H,3H)-Dione

(146) HBr (12.5 mL) was added to an AcOH (25 mL) solution containing 1-[4-(3-methoxyphenoxy)phenyl]dihydropyrimidine-2,4 (1H,3H)-dione (3.86 g) under ice-cooling, and the mixture was stirred for 3 hours. Water (100 mL) was added to the reaction solution, the mixture was stirred, and the precipitated crystals were collected by filtration. Washing with water and drying were performed, and purification through silica gel column chromatography (DCM/MeOH) was then performed, and the obtained solid was washed with MeOH to obtain the object compound (1.11 g).

#### Reference Example 77

##### Synthesis of 3-(3-Fluorophenoxy) Aniline

(147) A mixture containing 3-fluoroiodobenzene (0.587 mL), 3-aminophenol (818 mg), K.sub.3PO.sub.4 (2.12 g), picolinic acid (123 mg), copper iodide (I) (95 mg), and DMSO (15 mL) was stirred under a nitrogen atmosphere at 90° C. for 24 hours. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (865 mg).

#### Reference Example 83

##### Synthesis of 5-Nitro-2-Phenoxypyridine

(148) Sodium phenoxide (12.3 g) was added to a DMF (80 mL) solution containing 2-chloro-5-nitropyridine (16.0 g) while ice-cooling and stirring the solution and stirring was continued at room temperature overnight. The reaction solution was poured into ice water, and the precipitated crystals were collected by filtration and washed with water to obtain the object compound (21.1 g).

#### Reference Example 84

##### Synthesis of 6-Phenoxypyridin-3-Amine

(149) A mixture containing 5-nitro-2-phenoxypyridine (21 g), 10% Pd/C (2 g), and EtOH (200 mL) was stirred under a hydrogen atmosphere at room temperature for 3 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through



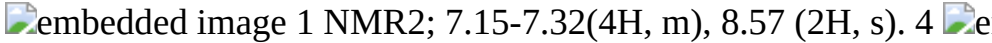



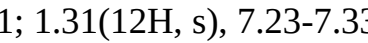
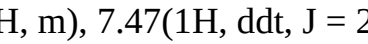
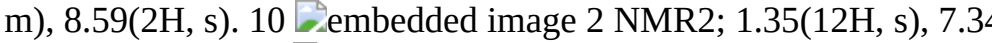
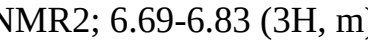
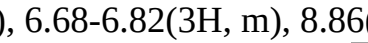
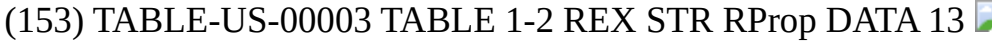
silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (15 g).


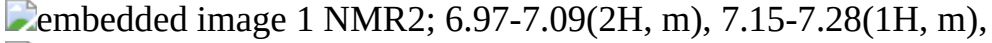
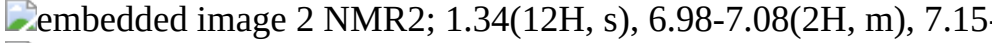
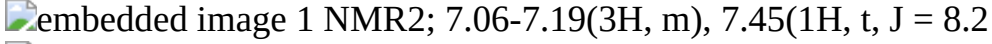
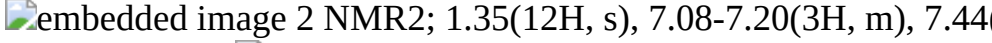
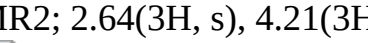
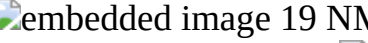
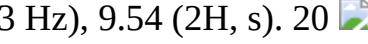
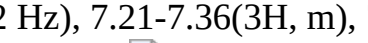

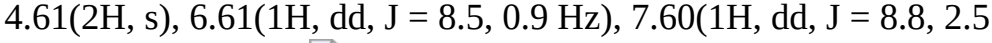
#### Reference Example 111



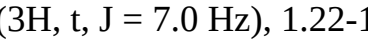
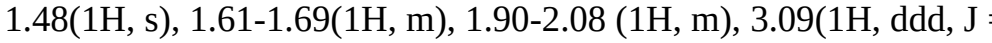

##### Synthesis of 1-(6-Chloropyridazine-3-Yl)Pyrimidine-2,4 (1H,3H)-Dione





(150) A mixture containing 3,6-dichloropyridazine (10.00 g), uracil (8.28 g), and DMSO (100 mL) was stirred at 70° C. overnight. Water was added to the reaction solution, and the generated solid was then collected by filtration, and washed with water and EtOH to obtain the object compound (9.51 g).











(151) The compounds of Reference Examples 3 to 17, 20, 27 to 34, 36, 37, 48, 49, 51 to 55, 57, 62 to 75, 78 to 82, 85 to 95 and 97 to 110 were manufactured in the same manner as in Reference Examples 1, 2, 18, 19, 21 to 26, 35, 38 to 47, 50, 56, 58 to 61, 76, 77, 83, 84 and 111. Structural formulae and physicochemical data of the compounds of Reference Examples 1 to 111 are shown in Tables 1-1 to 1-11.













(152) TABLE-US-00002 TABLE 1-1 REX STR RProp DATA 1  embedded image 1 NMR2; 7.14-7.23(2H, m), 7.24-7.33(1H, m), 7.39- 7.49(2H, m), 8.57(2H, s). 2  embedded image 2 NMR2; 1.34(12H, s), 7.17-7.22(2H, m), 7.23- 7.29(1H, m), 7.39-7.47(2H, m), 8.83(2H, s). 3  embedded image 1 NMR2; 7.15-7.32(4H, m), 8.57 (2H, s). 4  embedded image 2 NMR2; 1.34 (12H, s), 7.17-7.30(4H, m), 8.84(2H, s). 5  embedded image 1 NMR2; 6.90-7.04(3H, m), 7.39(1H, td, J = 8.3, 6.5 Hz), 8.58(2H, s). 6  embedded image 2 NMR2; 1.34(12H, s), 6.91-7.04(3H, m), 7.33- 7.44(1H, m), 8.85(2H, s). 7  embedded image 1 NMR2; 7.06-7.20(4H, m), 6.57(2H, s). 8  embedded image 2 NMR1; 1.31(12H, s), 7.23-7.33(4H, m), 8.75(2H, s). 9 0  embedded image 1 NMR2; 7.35-7.41(1H, m), 7.47(1H, ddt, J = 2.2, 1.5, 0.7 Hz), 7.51-7.61(2H, m), 8.59(2H, s). 10  embedded image 2 NMR2; 1.35(12H, s), 7.34-7.48(2H, m), 7.48- 7.60(2H, m), 8.85(2H, s). 11  embedded image 1 NMR2; 6.69-6.83 (3H, m), 8.60(2H, s). 12  embedded image 2 NMR2; 1.35(12H, s), 6.68-6.82(3H, m), 8.86(2H, s).


(153) TABLE-US-00003 TABLE 1-2 REX STR RProp DATA 13  embedded image 1 NMR2; 2.39(3H, s), 6.93-7.02(2H, m), 7.03- 7.13(1H, m), 7.26-7.37(1H, m), 8.56(2H, s). 14  embedded image 1 NMR2; 6.97-7.09(2H, m), 7.15-7.28(1H, m), 8.58(2H, s). 15  embedded image 2 NMR2; 1.34(12H, s), 6.98-7.08(2H, m), 7.15- 7.24(1H, m), 8.84(2H, s). 16  embedded image 1 NMR2; 7.06-7.19(3H, m), 7.45(1H, t, J = 8.2 Hz), 8.59(2H, s). 17  embedded image 2 NMR2; 1.35(12H, s), 7.08-7.20(3H, m), 7.44(1H, dt, J = 0.6, 8.1 Hz), 8.85(2H, s). 18  embedded image 18 NMR2; 2.64(3H, s), 4.21(3H, s), 7.11(1H, d, J = 9.2 Hz), 7.75(1H, d, J = 9.3 Hz), 9.14(2H, s). 19 0  embedded image 19 NMR2; 3.43(3H, s), 4.26(3H, s), 7.20(1H, d, J = 9.2 Hz), 7.89(1H, d, J = 9.3 Hz), 9.54 (2H, s). 20  embedded image 18 NMR2; 1.50(3H, t, J = 7.2 Hz), 4.58(2H, q, J = 7.2 Hz), 7.21-7.36(3H, m), 7.43-7.53(2H, m), 7.97(1H, d, J = 8.8 Hz), 8.30(1H, d, J = 8.8 Hz), 9.33(2H, s). 21  embedded image 21 NMR2; 2.61 (3H, s), 4.61(2H, s), 6.61(1H, dd, J = 8.5, 0.9 Hz), 7.60(1H, dd, J = 8.8, 2.5 Hz), 8.26(1H, dd, J = 2.5, 0.8 Hz), 8.67(2H, s). 22  embedded image 22 NMR1; 2.89(3H, s), 6.43(2H, s), 6.58(1H, dd, J = 8.7, 0.8 Hz), 7.91(1H, dd, J = 8.7, 2.5 Hz), 8.47(1H, dd, J = 2.6, 0.8 Hz), 9.24(2H, s). 23  embedded image 23 NMR2; 0.84-0.92(3H, m), 1.20-1.39(18H, m), 1.44(2H, t, J = 7.4 Hz), 1.71(2H, ddd, J = 15.1, 8.0, 6.8 Hz), 3.08-3.15(2H, m), 8.54(2H, s).

(154) TABLE-US-00004 TABLE 1-3 REX STR RProp DATA 24  embedded image 24 NMR2; 0.84-0.92 (3H, m), 1.26 (15H, s), 1.40-1.55 (2H, m), 1.75 (2H, m), 3.13-3.22(2H, m), 4.60 (2H, s), 6.61(1H, dd, J = 5.5, 0.9 Hz), 7.60 (1H, dd, J = 8.5, 2.5 Hz), 8.26(1H, dd, J = 2.5, 0.8 Hz), 8.65(2H, s). 25  embedded image 25 NMR2; 0.88(3H, t, J = 7.0 Hz), 1.22-1.34(16H, m), 1.35-1.51(1H, m), 1.48(1H, s), 1.61-1.69(1H, m), 1.90-2.08 (1H, m), 3.09(1H, ddd, J = 13.1, 9.8, 5.2 Hz), 3.17 (1H, ddd, J = 13.1, 9.9, 6.2 Hz), 4.73(2H, s), 6.65(1H, dd, J = 8.6, 0.8 Hz), 7.69 (1H, dd, J = 8.6, 2.5 Hz), 5.36 (1H, dd, J = 2.6, 0.8 Hz), 8.98(2H, s). 26  embedded image 26 NMR2; 5.64(2H, s), 7.15(1H, d, J = 9.2 Hz), 7.21- 7.54(10H, m), 7.75(1H, d, J = 9.2 Hz), 9.17(2H, s). 27  embedded image 18 NMR2; 5.65(2H, s), 6.96-7.10(3H, m), 7.16(1H, d, J = 9.2 Hz), 7.32-7.48(4H, m), 7.48-7.56(2H, m), 7.76(1H, d, J = 9.2 Hz), 9.18(2H, s). 28  embedded image 18


NMR2; 5.64(2H, s), 7.16(1H, d, J = 9.2 Hz), 7.18- 7.45(7H, m), 7.48-7.56(2H, m), 7.75(1H, d, J = 9.2 Hz), 9.17(2H, s). 29 0  embedded image 18 NMR2; 5.64(2H, s), 7.09-7.27(5H, m), 7.32-7.46(3H, m), 7.48-7.56(2H, m), 7.75(1H, d, J = 9.2 Hz), 9.16(2H, s). 30  embedded image 18 NMR2; 5.65(2H, s), 7.17(1H, d, J = 9.2 Hz), 7.33- 7.62(9H, m), 7.77(1H, d, J = 9.2 Hz), 9.18(2H, s). 31  embedded image 18 NMR2; 5.65(2H, s), 7.02-7.09(2H, m), 7.15(1H, d, J = 9.2 Hz), 7.19-7.28(1H, m), 7.34-7.45(3H, m), 7.50-7.55(2H, m), 7.76(1H, d, J = 9.2 Hz), 9.17(2H, s). 32  embedded image 18 NMR2; 5.85(2H, s), 6.73-6.80(1H, m), 6.81- 6.87(2H, m), 7.17(1H, d, J = 9.2 Hz), 7.34-7.45(3H, m), 7.50-7.55(2H, m), 7.77(1H, d, J = 9.2 Hz), 9.19(2H, s).








(155) TABLE-US-00005 TABLE 1-4 REX STR RProp DATA 33  embedded image 18 NMR2; 5.43(2H, s), 6.93(1H, dd, J = 0.8, 8.6 Hz), 7.17-7.51 (10H, m), 7.73(1H, dd, J = 2.6, 8.6 Hz), 8.33(1H, dd, J = 0.8, 2.6 Hz), 8.70(2H, s). 34  embedded image 18 NMR2; 3.98(3H, s), 7.02(1H, dd, J = 5.0, 7.4 Hz), 7.17-7.33(3H, m), 7.40-7.51(2H, m), 7.61(1H, dd, J = 1.9, 7.4 Hz), 8.22(1H, dd, J = 1.9, 5.0 Hz), 8.76(2H, s). 35  embedded image 35 NMR2; 1.57-1.85(4H, m), 2.04-2.10(1H, m), 2.13- 2.27(1H, m), 3.73-3.84(1H, m), 4.13-4.22(1H, m), 6.15(1H, dd, J = 2.2, 10.7 Hz), 7.18-7.34(4H, m), 7.41-7.51(2H, m), 7.96(1H, d, J = 4.1 Hz), 9.01(2H, s). 36  embedded image 18 NMR2; 1.57-1.64(1H, m), 1.66-1.84(3H, m), 2.04- 2.11(1H, m), 2.13-2.28(1H, m), 3.73-3.85(1H, m), 4.13-4.22(1H, m), 6.16(1H, dd, J = 2.2, 10.7 Hz), 6.94-7.08(3H, m), 7.31(1H, d, J = 4.1 Hz), 7.35- 7.46(1H, m), 7.96(1H, d, J = 4.1 Hz), 9.02(2H, s). 37  embedded image 18 NMR2; 1.59-1.86(4H, m), 2.05(1H, d, J = 5.7 Hz), 2.13-2.27(1H, m), 3.73-3.84(1H, m), 4.13- 4.22(1H, m), 6.15(1H, dd, J = 2.2, 10.7 Hz), 7.17- 7.35(6H, m), 7.95(1H, d, J = 4.1 Hz), 9.01(2H, s). 38  embedded image 38 NMR2; 1.12(18H, d, J = 7.5 Hz), 1.91(3H, hept. J = 7.5 Hz), 8.16(2H, d, J = 2.2 Hz), 8.51(1H, d, J = 2.2 Hz). 39 0  embedded image 39 NMR2; 1.33(12H, s), 3.94(3H, s), 7.15-7.28(3H, m), 7.36-7.46(2H, m), 8.56(1H, s). 40  embedded image 40 NMR2; 0.84-0.92(3H, m), 1.23-1.36(28H, m), 1.40-1.48(2H, m), 1.66-1.78(2H, m), 3.11-3.21(2H, m), 8.75(2H, s). 41  embedded image 41 NMR2; 0.84-0.92(3H, m), 1.27(16H, d, J = 4.9 Hz), 1.42-1.66(2H, m), 1.70-1.83(2H, m), 3.15- 3.24(2H, m), 7.32(1H, dd, J = 9.3, 1.8 Hz), 7.68-7.79(3H, m), 8.31 (1H, dd, J = 1.8, 1.0 Hz), 8.71(2H, s). 42  embedded image 42 NMR2; 0.88-0.92(3H, m), 1.25(16H, s), 1.47(2H, q, J = 7.4 Hz), 1.83-1.93(2H, m), 3.52-3.61(2H, m), 7.40(1H, dd, J = 9.3, 1.9 Hz), 7.74-7.80 (2H, m), 7.82-7.87 (1H, m), 8.45-8.51(1H, m), 9.14(2H, s).










(156) TABLE-US-00006 TABLE 1-5 REX STR RProp DATA 43  embedded image 1 NMR2; 7.17-7.24(2H, m), 7.31-7.39(1H, m), 7.45- 7.53(2H, m), 9.33(2H, s). 44  embedded image 44 NMR2; 3.50(2H, brs), 7.13-7.24(3H, m), 7.35- 7.45(2H, m), 8.07(2H, s). 45  embedded image 45 NMR2; 2.05(2H, p, J = 6.5 Hz), 3.47(2H, q, J = 6.4 Hz), 3.60-3.68(2H, m), 4.74(1H, s), 6.10(1H, s), 7.15- 7.27(3H, m), 7.35-7.47(2H, m), 8.60(2H, s). 46  embedded image 46 NMR2; 6.93-7.12(3H, m), 7.61(1H, dt, J = 6.4 Hz, 8.3 Hz), 9.34(2H, s). 47  embedded image 47 NMR2; 3.66(2H, brs), 8.86-7.00(8H, m), 7.30- 7.39(1H, m), 8.08(2H, s). 48  embedded image 10 NMR2; 1.82-1.98(4H, m), 2.47(2H, t, J = 8.9 Hz), 3.55-3.63(2H, m), 6.90-7.03(3H, m), 7.16(1H, s), 7.32-7.43(1H, m), 8.76(2H, s). 49 0  embedded image 11 NMR2; 1.06(21H, d, J = 2.0 Hz), 1.37-1.63(3H, m), 1.76-1.87(2H, m), 2.61(2H, ddd, J = 12.5, 9.3, 3.1 Hz), 3.02-3.13(2H, m), 3.79-3.90(1H, m). 50  embedded image 50 NMR2; 1.07(21H, d, J = 3.5 Hz), 1.70-1.80(2H, m), 1.93(2H, ddt, J = 12.0, 7.6, 3.5 Hz), 3.04(2H, ddd, J = 11.6, 7.1, 3.7 Hz), 3.36(2H, ddd, J = 11.9, 8.3, 3.5 Hz), 3.98-4.08(1H, m), 7.14-7.25(3H, m), 7.35- 7.45(2H, m), 8.23(2H, s). 51  embedded image 50 NMR2; 1.07(21H, d, J = 3.6 Hz), 1.71-1.83(2H, m), 1.87-1.99(2H, m), 3.07(2H, ddd, J = 11.5, 7.0, 3.8 Hz), 3.35(2H, ddd, J = 11.9, 8.3, 3.5 Hz), 4.04(1H, tt, J = 6.7, 3.3 Hz), 6.86-7.01(3H, m), 7.29-7.40 (1H, m), 8.24(2H, s). 52  embedded image 50 NMR2; 1.00-1.15(21H, m), 1.70-1.83(2H, m), 1.86-1.99(2H, m), 3.00-3.09(2H, m), 3.29- 3.40(2H, m), 3.98-4.08(1H, m), 7.02-7.19(4H, m), 8.22(2H, s). 53  embedded image 1 NMR2; 7.14-7.22(2H, m), 7.23-7.34(1H, m), 7.39- 7.49(2H, m), 8.88(2H, s). 54  embedded image 1 NMR2; 6.90-7.04(3H, m), 7.29-7.44(1H, m), 8.70(2H, s).




(157) TABLE-US-00007 TABLE 1-6 REX STR RProp DATA 55  embedded image 1 NMR2;
























05-7.24(4H, m), 8.68(2H, s). 56  embedded image 56 NMR2; 1.02-1.18(21H, m), 2.08(2H, dddd, J = 15.4, 10.2, 5.7, 2.2 Hz), 2.61-2.71(1H, m), 2.75(1H, dd, J = 17.4, 3.9 Hz), 3.48-3.58(1H, m), 3.91-4.02(1H, m), 4.46(1H, ddd, J = 6.8, 5.3, 3.3 Hz), 7.16- 7.31(3H, m), 7.39-7.49(2H, m), 8.50(2H, s). 57  embedded image 18 NMR2; 7.20-7.28(2H, m), 7.26-7.36(1H, m), 7.42- 7.53(2H, m), 7.66-7.74(2H, m), 8.32-6.41 (2H, m), 8.81(2H, s).






(158) TABLE-US-00008 TABLE 1-7 REX STR RProp DATA 58  embedded image 58 NMR2; 6.82(1H, dt, J = 9.5, 2.3 Hz), 6.85-6.90(1H, m), 6.96(1H, tdd, J = 8.3, 2.5, 0.9 Hz), 7.01- 7.10(2H, m), 7.39(1H, td, J = 8.3, 6.5 Hz), 8.19- 8.28(2H, m) 59 0  embedded image 59 NMR2; 3.61(2H, s), 6.61(1H, dt, J = 10.6, 2.4 Hz), 6.64-6.76(4H, m), 6.83-6.94(2H, m), 7.20(2H, td, J = 8.3, 6.7 Hz) 60  embedded image 60 NMR1; 2.71(2H, t, J = 6.7 Hz), 3.79(2H, t, J = 6.7 Hz), 7.28-7.32(2H, m), 7.56-7.60(2H, m), 10.43(1H, s). 61  embedded image 61 NMR1; 1.29(12H, s), 2.71(2H, t, J = 6.6 Hz), 3.82(2H, t, J = 6.6 Hz), 7.35(2H, d, J = 8.4 Hz), 7.68(2H, d, J = 8.4 Hz), 10.41(1H, s). 62  embedded image 58 NMR2; 6.96-6.99(1H, m), 7.01-7.14(4H, m), 7.45(1H, t, J = 8.3 Hz), 8.20-8.29(2H, m) 63  embedded image 59 NMR2; 3.83(2H, brs), 6.66-6.73(2H, m), 6.75- 6.79(1H, m), 6.81-6.92(4H, m), 7.26(1H, t, J = 8.3 Hz) 64  embedded image 58 NMR2; 7.02-7.10(2H, m), 7.24-7.31(1H, m), 7.34-7.38(1H, m), 7.48-7.60(2H, m), 6.21- 6.28(2H, m) 65  embedded image 59 NMR2; 3.63(2H, s), 6.66-6.74(2H, m), 6.83- 6.92(2H, m), 7.05-7.11(1H, m), 7.12-7.18(1H, m), 7.21-7.32(1H, m), 7.38-7.42(1H, m) 66  embedded image 58 NMR2; 6.98-7.05(2H, m), 7.15-7.31(4H, m), 8.18- 8.24(2H, m). 67  embedded image 59 NMR2; 3.57(2H, br), 6.64-6.71(2H, m), 6.83- 6.88(2H, m), 6.88-6.95(1H, m), 6.96-7.05(2H, m), 7.10-7.17(1H, m). 68  embedded image 58 NMR2; 6.95-7.02(2H, m), 7.03-7.17(4H, m), 8.16- 8.25(2H, m). 69 00  embedded image 59 NMR2; 3.51(2H, br), 6.66-6.70(2H, m), 6.80- 6.92(4H, m), 6.93-7.00(2H, m).

(159) TABLE-US-00009 TABLE 1-8 REX STR RProp DATA 70 01  embedded image 58 NMR2; 3.81(3H, s), 6.64(1H, dd, J = 2.3, 2.3 Hz), 6.67(1H, ddd, J = 0.8, 2.2, 8.0 Hz), 5.80(1H, ddd, J = 0.8, 2.4, 8.3 Hz), 7.00-7.06(2H, m), 7.33(1H, dd, J = 8.2, 8.2 Hz), 8.18-8.23(2H, m). 71 02  embedded image 59 NMR2; 3.58(2H, br), 3.75(3H, s), 6.49-6.51(2H, m), 6.55-6.58(1H, m), 6.63-6.59(2H, m), 6.85- 6.89(2H, m), 7.14-7.18(1H, m). 72 03  embedded image 58 NMR2; 7.11-7.18(1H, m), 7.19-7.23(1H, m), 7.23- 7.28(2H, m), 7.28-7.33(1H, m), 7.38-7.46(1H, m), 8.08-8.24(2H, m). 73 04  embedded image 59 NMR2; 3.87(2H, br), 6.67-6.79(4H, m), 6.85- 6.90(1H, m), 7.12-7.19(1H, m), 7.30-7.35(2H, m). 74 05  embedded image 58 NMR2; 7.15-7.21(2H, m), 7.43-7.50(3H, m), 7.52- 7.58(2H, m), 8.04-8.09(2H, m). 75 06  embedded image 59 NMR1; 5.52(2H, s), 6.59-6.64(2H, m), 6.98- 7.03(2H, m), 7.06-7.12(1H, m), 7.16-7.20(2H, m), 7.20-7.27(2H, m). 76 07  embedded image 76 NMR1; 2.71(2H, t, J = 6.7 Hz), 3.77(2H, t, J = 6.7 Hz), 6.37(1H, dd, J = 2.3, 2.3 Hz), 6.44(1H, ddd, J = 0.8, 2.3, 8.1 Hz), 6.53(1H, ddd, J = 0.8, 2.2, 8.1 Hz), 7.00-7.06(2H, m), 7.16(1H, dd, J = 8.1, 8.1 Hz), 7.31-7.36(2H, m), 9.61(1H, s), 10.37(1H, s) 77 08  embedded image 77 NMR2; 3.72(2H, br), 6.35(1H, dd, J = 2.2, 2.2 Hz), 6.41(1H, ddd, J = 0.8, 2.3, 8.1 Hz), 6.48(1H, ddd, J = 0.8, 2.2, 8.0 Hz), 6.71(1H, ddd, J = 2.4, 2.4, 6.9 Hz), 6.74-6.82(2H, m), 7.12(1H, dd, J = 8.0, 8.0 Hz), 7.21-7.29(1H, m). 78 09  embedded image 77 NMR2; 3.61(2H, br), 8.88-5.74(2H, m), 6.56(1H, ddd, J = 0.8, 0.8, 6.5 Hz), 6.91-6.97(3H, m), 7.63(1H, ddd, J = 1.8, 7.2, 8.3 Hz), 8.18(1H, ddd, J = 0.8, 2.0, 5.0 Hz). 79 0  embedded image 58 NMR2; 7.09-7.17(4H, m), 7.79-7.85(2H, m), 8.24- 8.30(2H, m). 80  embedded image 59 NMR2; 3.68(2H, br), 6.68-6.74(2H, m), 6.85- 6.94(4H, m), 7.62-7.67(2H, m). 81  embedded image 58 NMR2; 7.03-7.09(2H, m), 7.36-7.47(2H, m), 8.21- 8.28(2H, m), 8.49(1H, d, J = 2.5 Hz), 6.53(1H, dd, J = 1.5, 4.5 Hz).

(160) TABLE-US-00010 TABLE 1-9 REX STR RProp DATA 82  embedded image 59 NMR2; 3.64(2H, br), 6.67-6.72(2H, m), 6.85- 6.91(2H, m), 7.20-7.23(2H, m), 8.28-8.31(1H, m), 8.35-8.38(1H, m). 83  embedded image 83 NMR2; 7.03(1H, dd, J = 9.0, 0.6 Hz), 7.13-7.20(2H, m), 7.27-7.34(1H, m), 7.42-7.50(2H, m), 8.48(1H, dd, J = 9.0, 2.8 Hz), 9.03-9.07(1H, m). 84  embedded image 84 NMR2; 3.53(2H, brs), 6.72-6.79(1H, m), 7.01- 7.16(4H, m), 7.29-7.39(2H, m), 7.69-7.75(1H, m). 85  embedded image 58 NMR2; 2.60(3H, s), 6.80-6.85(2H, m), 7.03-

7.12(2H, m), 7.20-7.29(1H, m), 7.37-7.48(2H, m), 8.01-8.09(1H, m). 86  embedded image 59 NMR2; 2.15(3H, s), 3.50(2H, brs), 6.65(1H, d, J = 8.4 Hz), 6.71-6.82(2H, m), 6.86-6.97(2H, m), 7.00(1H, tt, J = 7.3, 1.1 Hz), 7.22-7.32(2H, m). 87  embedded image 58 NMR2; 3.90(3H, s), 6.49(1H, dd, J = 9.1, 2.4 Hz), 6.66(1H, d, J = 2.4 Hz), 7.05-7.13(2H, m), 7.20- 7.38(1H, m), 7.38-7.49(2H, m), 7.94(1H, d, J = 9.1 Hz). 88  embedded image 59 NMR2; 3.68(2H, s), 3.79(3H, s), 6.46-6.54(1H, m), 6.54-6.60(1H, m), 6.67(1H, d, J = 8.3 Hz), 6.89- 6.97(2H, m), 6.97-7.05(1H, m), 7.23-7.33(2H, m). 89  embedded image 58 NMR2; 2.87(3H, d, J = 0.8 Hz), 6.80-6.86(1H, m), 7.10-7.18(2H, m), 7.25-7.33(1H, m), 7.39- 7.51(2H, m), 8.89(1H, s). 90  embedded image 59 NMR2; 2.15-2.21(3H, m), 3.44(2H, s), 5.66(1H, s), 6.99-7.07(2H, m), 7.07-7.14(1H, m), 7.28-7.38(2H, m), 7.56(1H, d, J = 1.6 Hz). 91  embedded image 58 NMR2; 2.76(3H, s), 6.78(1H, dd, J = 8.9, 0.7 Hz), 7.12-7.20(2H, m), 7.23-7.32(1H, m), 7.40- 7.48(2H, m), 8.36(1H, d, J = 8.9 Hz) 92  embedded image 59 NMR2; 2.32-2.37(3H, m), 3.46(2H, s), 8.56(1H, d, J = 8.3 Hz), 6.94-7.12(4H, m), 7.27-7.36(2H, m). 93  embedded image 58 NMR2; 6.97(1H, dd, J = 9.1, 7.9 Hz), 7.06-7.14(2H, m), 7.21-7.32(1H, m), 7.38-7.49(2H, m), 7.98(1H, ddd, J = 9.1, 2.7, 1.5 Hz), 8.09(1H, dd, J = 10.3, 2.7 Hz). 94  embedded image 59 NMR2; 3.67(2H, bs), 6.40(1H, ddd, J = 8.6, 2.7, 1.2 Hz), 6.49(1H, dd, J = 12.0, 2.7 Hz), 6.86-6.96(3H, m), 5.96-7.06(1H, m), 7.22-7.32(2H, m).

(161) TABLE-US-00011 TABLE 1-10 REX STR RProp DATA 95  embedded image 58 NMR2; 6.90-7.01(2H, m), 7.10-7.21(1H, m), 7.30- 7.41(2H, m), 7.90-8.01(2H, m). 96  embedded image 59 NMR2; 3.78(2H, s), 6.23-6.34(2H, m), 6.87- 5.98(2H, m), 6.96-7.09(1H, m), 7.21-7.34(2H, m). 97  embedded image 58 NMR2; 6.93(1H, dt, J = 9.4, 2.3 Hz), 6.96-7.05(2H, m), 7.07(1H, dd, J = 9.0, 0.6 Hz), 7.42(1H, td, J = 8.3, 6.5 Hz), 8.50(1H, dd, J = 9.0, 2.8 Hz), 9.05(1H, dd, J = 2.9, 0.6 Hz). 98  embedded image 59 NMR2; 3.48(2H, brs), 8.82(1H, dd, J = 8.6, 0.7 Hz), 7.05-7.22(5H, m), 7.64(1H, dd, J = 3.0, 0.7 Hz). 99  embedded image 58 NMR2; 6.59-7.05(3H, m), 7.07(1H, dd, J = 9.0, 0.6 Hz), 7.42(1H, td, J = 8.3, 6.5 Hz), 8.50(1H, dd, J = 9.0, 2.8 Hz), 9.05(1H, dd, J = 2.9, 0.6 Hz) 100  embedded image 59 NMR2; 3.58(2H, brs), 6.72-6.87(4H, m), 7.10(1H, ddd, J = 8.6, 3.0, 1.5 Hz), 7.22-7.33(1H, m), 7.70- 7.78(1H, m). 101  embedded image 58 NMR2; 7.06-7.15(1H, m), 7.34-7.41(1H, m), 7.42- 7.47(1H, m), 7.52-7.63(2H, m), 8.52(1H, dd, J = 9.0, 2.8 Hz), 9.03(1H, dd, J = 2.8, 0.6 Hz). 102  embedded image 59 NMR2; 3.59(2H, s), 6.78-6.85(1H, m), 7.07- 7.15(1H, m), 7.19-7.25(1H, m), 7.28-7.32(1H, m), 7.33-7.39(1H, m), 7.44(1H, t, J = 7.8 Hz), 7.69- 7.75(1H, m). 103  embedded image 58 NMR2; 2.61(3H, s), 6.80(1H, dt, J = 9.5, 2.4 Hz), 6.83-6.91(3H, m), 6.94(1H, tdd, J = 8.3, 2.5, 0.9 Hz), 7.37(1H, td, J = 8.3, 6.5 Hz), 8.03-8.10(1H, m). 104  embedded image 59 NMR2; 2.16(3H, s), 3.54(2H, s), 6.60(1H, dt, J = 10.7, 2.4 Hz), 6.64-6.81(8H, m), 7.20(1H, td, J = 8.3, 6.7 Hz). 105  embedded image 58 NMR2; 2.62(3H, s), 6.84-6.93(2H, m), 7.21- 7.29(1H, m), 7.33(1H, dq, J = 2.3, 0.7 Hz), 7.45- 7.59(2H, m), 8.08(1H, d, J = 8.8 Hz). 106  embedded image 59 NMR2; 2.17(3H, s), 3.56(2H, s), 6.68(1H, d, J = 8.4 Hz), 6.72-6.82(2H, m), 7.04-7.11(1H, m), 7.12-7.18(1H, m), 7.20-7.30(1H, m), 7.32- 7.41(1H, m).

(162) TABLE-US-00012 TABLE 1-11 REX STR RProp DATA 107  embedded image 58 NMR2; 2.61(3H, s), 6.85-6.93(2H, m), 6.93- 6.98(1H, m), 7.00(1H, ddd, J = 8.2, 2.3, 0.9 Hz), 7.05-7.14(1H, m), 7.43(1H, t, J = 8.3 Hz), 8.04- 8.11(1H, m). 108  embedded image 59 NMR2; 2.16(3H, s), 3.55(2H, s), 6.67(1H, d, J = 8.4 Hz), 6.72-6.89(5H, m), 7.25(1H, t, J = 8.3 Hz). 109  embedded image 58 NMR2; 6.81(1H, d, J = 8.6 Hz), 6.90(1H, ddd, J = 2.3, 2.3, 9.5 Hz), 6.93-7.03(2H, m), 7.42(1H, ddd, J = 6.5, 8.3, 8.3 Hz), 7.65-7.71 (1H, m), 7.81 (1H, ddd, J = 1.4, 7.1, 8.6 Hz), 8.27(1H, d, J = 8.6 Hz), 8.45(1H, d, J = 8.4 Hz), 8.76(1H, d, J = 8.8 Hz). 110  embedded image 59 NMR2; 4.11(2H, br), 6.62(1H, ddd, J = 2.4, 2.4, 10.6 Hz), 6.66-6.77(3H, m), 7.00(1H, d, J = 8.0 Hz), 7.20(1H, ddd, J = 6.7, 6.7, 8.3 Hz), 7.43-7.54(2H, m), 7.83-7.89(1H, m), 7.93-7.98(1H, m). 111  embedded image 111 NMR2; 5.85(1H, d, J = 8.1 Hz), 8.07-8.24(3H, m), 11.73(1H, s).

## EXAMPLES

### Example 1

#### Synthesis of 3-Methoxy-6-(2-Phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine

(163) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (5.00 g), 3-chloro-6-methoxypyridazine (3.64 g), PdCl.sub.2 (dppf) DCM (0.137 g), K.sub.3PO.sub.4 (7.12 g), 1,4-dioxane (50 mL), and water (25 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (4.42 g).

#### Example 4

##### Synthesis of 3-(2-(3-Fluorophenoxy)Pyrimidin-5-Yl)-6-Methoxypyridazine

(164) A mixture containing 5-bromo-2-(3-fluorophenoxy)pyrimidine (2.234 g), (BPin).sub.2 (2.63 g), PdCl.sub.2 (dppf) DCM (0.282 g), AcOK (1.358 g), and 1,4-dioxane (20 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. 3-Chloro-6-methoxypyridazine (1.00 g), PdCl.sub.2 (dppf) DCM (0.282 g), K.sub.3PO.sub.4 (2.94 g), and water (5 mL) were added to the reaction solution and the mixture was heated to reflux under a nitrogen atmosphere overnight. Water and AcOEt were added to the reaction solution, the mixture was filtered through Celite, and the product was then extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The precipitated crystals were washed with EtOH to obtain the object compound (947 mg).

#### Example 6

##### Synthesis of 5-(6-Methoxypyridin-3-Yl)-2-Phenoxypyrimidine

(165) A mixture containing 5-bromo-2-phenoxypyrimidine (1.0 g), 2-methoxy-5-pyridineboronic acid (0.914 g), PdCl.sub.2 (dppf) DCM (0.163 g), K.sub.3PO.sub.4 (1.691 g), 1,4-dioxane (10 mL), and water (5 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt), and the obtained solid was washed with EtOH to obtain the object compound (821 mg).

#### Example 7

##### Synthesis of 2-Phenoxy-5-(Pyridin-3-Yl)Pyrimidine

(166) A mixture containing 5-bromo-2-phenoxypyrimidine (1.0 g), 3-pyridineboronic acid (0.734 g), PdCl.sub.2 (dppf) DCM (0.163 g), K.sub.3PO.sub.4 (1.691 g), 1,4-dioxane (10 mL), and water (5 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt), and the obtained solid was washed with EtOH to obtain the object compound (386 mg).

#### Example 11

##### Synthesis of 3-(2-Phenoxypyrimidin-5-Yl)Pyridine 1-Oxide

(167) A mixture containing 2-phenoxy-5-(pyridin-3-yl)pyrimidine (749 mg), hydrous 77% m-CPBA (1,616 mg), and DCM (15 mL) was stirred at room temperature overnight. Dimethyl sulfide (309 µl) was added to the reaction solution and stirred for some time, and a saturated NaHCO.sub.3 aqueous solution was then added thereto, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and the obtained solid was washed with AcOEt to obtain the object compound (118 mg).

#### Example 24

##### Synthesis of 6-(2-(3-Fluorophenoxy)Pyrimidin-5-Yl)Pyridazin-3-Amine

(168) A mixture containing 2-(3-fluorophenoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (581 mg), 3-amino-6-chloropyridazine (202 mg), K.sub.3PO.sub.4 (1.11 g),

PdCl.sub.2 (dppf) DCM (68 mg), 1,4-dioxane (20 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt, AcOEt/MeOH), and the obtained solid was washed with IPE to obtain the object compound (100 mg).

#### Example 30

##### Synthesis of 6-(2-Phenoxyimidin-5-Yl)Pyridazin-3-Amine

(169) A mixture containing 3-amino-6-chloropyridazine (205 mg), 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (526 mg), K.sub.3PO.sub.4 (1.11 g), PdCl.sub.2 (dppf) DCM (65.2 mg), 1,4-dioxane (10 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 5 hours and a half. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt, AcOEt/MeOH) to obtain the object compound (180 mg).

#### Example 36

##### Synthesis of 5-(2-Phenoxyimidin-5-Yl)Pyridin-2-Amine

(170) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (386 mg), 2-amino-5-bromopyridine (209 mg), K.sub.3PO.sub.4 (1.0 g), PdCl.sub.2 (dppf) DCM (43.7 mg), 1,4-dioxane (20 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 2.75 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and then dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt), and the obtained solid was washed with IPE to obtain the object compound (161 mg).

#### Example 38

##### Synthesis of 3-(2-Phenoxyimidin-5-Yl)-6-(Trifluoromethyl)Pyridazine

(171) A mixture containing 3-chloro-6-(trifluoromethyl)pyridazine (209 mg), 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (373 mg), K.sub.3PO.sub.4 (780 mg), PdCl.sub.2 (dppf) DCM (29.3 mg), 1,4-dioxane (20 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 5 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and then dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt), and the obtained solid was washed with AcOEt to obtain the object compound (107 mg).

#### Example 60

##### Synthesis of 3-(2-(2-Fluorophenoxy)Imidin-5-Yl)Pyridine 1-Oxide

(172) A mixture containing 3-(2-(2-fluorophenoxy)imidin-5-yl)pyridine (998 mg), hydrous 77% m-CPBA (1,255 mg), and DCM (15 mL) was stirred at room temperature overnight. Dimethyl sulfide and a saturated NaHCO.sub.3 aqueous solution were added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (AcOEt/MeOH), and the obtained solid was washed with EtOH to obtain the object compound (383 mg).

#### Example 63

##### Synthesis of 3-(2-(2,5-Difluorophenoxy)Imidin-5-Yl)-6-Methoxypyridazine

(173) A mixture containing 2,5-difluorophenol (132 mg), 3-methoxy-6-(2-(methylsulfonyl)imidin-5-yl)pyridazine (167 mg), K.sub.2CO.sub.3 (176 mg), and DMF (5 mL) was stirred at room temperature for 2 hours. Water was added to the reaction solution, and the precipitated crystals were then collected by filtration to obtain the object compound (187 mg).



#### Example 69

##### Synthesis of 2-(6-(2-Phenoxy pyrimidin-5-Yl)Pyridazin-3-Yl) Propan-2-ol

(174) Ethyl 6-(2-phenoxy pyrimidin-5-yl)pyridazine-3-carboxylate (200 mg) was suspended in THF (3 mL), a THF solution (1.6 mL) containing 0.96 M methyl magnesium bromide was then added thereto under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction solution was poured into a saturated ammonium chloride aqueous solution, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate, and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and the obtained solid was washed with IPE to obtain the object compound (45 mg).

#### Example 72

##### Synthesis of (6-(2-Phenoxy pyrimidin-5-Yl)Pyridazin-3-Yl) Methanol

(175) Ethyl 6-(2-phenoxy pyrimidin-5-yl)pyridazine-3-carboxylate (400 mg) was added to a mixture containing calcium chloride (551 mg), NaBH<sub>4</sub> (117 mg), THF (2 mL), and EtOH (2 mL) under ice-cooling, and the mixture was stirred for 30 minutes. A citric acid aqueous solution was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and the obtained solid was washed with IPE to obtain the object compound (81 mg).

#### Example 84

##### Synthesis of 5-(2-(2,5-Difluorophenoxy)Pyrimidin-5-Yl)Pyridin-2-Amine

(176) A mixture containing 5-(2-(methylsulfinyl)pyrimidin-5-yl)pyridin-2-amine (100 mg), 2,5-difluorophenol (130 mg), K<sub>2</sub>CO<sub>3</sub> (236 mg), and DMF (7 mL) was stirred under a nitrogen atmosphere at 80° C. for 3.5 hours. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel chromatography (Hexane/AcOEt), and the obtained solid was washed with Hexane/IPE to obtain the object compound (44 mg).

#### Example 88

##### Synthesis of 5-(2-(m-Tolyloxy)Pyrimidin-5-Yl)Pyridin-2-Amine

(177) A mixture containing 5-(2-(dodecylsulfinyl)pyrimidin-5-yl)pyridin-2-amine (163 mg), m-cresol (0.10 mL), K<sub>2</sub>CO<sub>3</sub> (483 mg), and DMF (10 mL) was stirred under a nitrogen atmosphere at 80° C. for 4 hours. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel chromatography (Hexane/AcOEt), and the obtained solid was washed with IPE to obtain the object compound (50 mg).

#### Example 91

##### Synthesis of 6-(2-Phenoxy pyrimidin-5-Yl)Pyridazin-3 (2H)-One

(178) A mixture containing 3-(benzyloxy)-6-(2-phenoxy pyrimidin-5-yl)pyridazine (2.54 g), 10% Pd/C (2 g), EtOH (25 mL), and THF (75 mL) was stirred under a hydrogen atmosphere at room temperature for 3 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was crystallized from EtOH to obtain the object compound (1.38 g).

#### Example 92

##### Synthesis of 6-(2-Phenoxy pyrimidin-5-Yl)-4,5-Dihydropyridazin-3 (2H)-One

(179) A mixture containing 6-(2-phenoxy pyrimidin-5-yl)pyridazin-3 (2H)-one (1.08 g), zinc powder (0.53 g), and AcOH (10 mL) was heated to reflux for 1 hour. The reaction solution was concentrated, water was added to the residue, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then

concentrated. The residue was purified through silica gel column chromatography (DCM/MeOH) and then washed with EtOH to obtain the object compound (583 mg).

#### Example 94

##### Synthesis of 6-(2-(3-Fluorophenoxy)Pyrimidin-5-Yl)-4,5-Dihydropyridazin-3 (2H)-One

(180) A mixture containing 6-(2-(3-fluorophenoxy)pyrimidin-5-yl)pyridazin-3 (2H)-one (1.02 g), zinc powder (0.56 g), and AcOH (10 mL) was heated to reflux for 3 hours. The reaction solution was concentrated, water was added to the residue, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt), and the obtained solid was washed with EtOH to obtain the object compound (587 mg).

#### Example 106

##### Synthesis of 5-(2-(m-Tolyloxy)Pyrimidin-5-Yl)Pyridin-2 (1H)-One

(181) A mixture containing 5-(6-methoxypyridin-3-yl)-2-(m-tolyloxy)pyrimidine (425 mg), sodium iodide (652 mg), chlorotrimethylsilane (0.552 mL), and MeCN (5 mL) was stirred at room temperature overnight. Water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate, and then concentrated. The residue was: purified through silica gel column chromatography (DCM/MeOH) and then crystallized from EtOH to obtain the object compound (204 mg).

#### Example 114

##### Synthesis of 4-(2-Phenoxypyrimidin-5-Yl)Pyridazin-3 (2H)-One

(182) A mixture containing 4-(2-phenoxypyrimidin-5-yl)-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3 (2H)-one (1.085 g), TFA (10 mL), and DCM (10 mL) was stirred at room temperature for 1 hour. The reaction solution was concentrated, a saturated NaHCO<sub>3</sub> aqueous solution was added to the residue for neutralization, and the product was then extracted with DCM. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt), and the obtained solid was then washed with EtOH to obtain the object compound (672 mg).

#### Example 118

##### Synthesis of 4-(2-Phenoxypyrimidin-5-Yl) Quinoline

(183) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (500 mg), 4-bromoquinoline (419 mg), K<sub>3</sub>PO<sub>4</sub> (712 mg), PdCl<sub>2</sub>(dppf) DCM (13.70 mg), 1,4-dioxane (5 mL), and water (2.5 mL) was heated to reflux under a nitrogen atmosphere for 1.5 hours. Water was added to the reaction solution, the product was extracted with AcOEt. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and the obtained solid was washed with IPE to obtain the object compound (413 mg).

#### Example 119

##### Synthesis of 6-(2-Phenoxypyrimidin-5-Yl) Imidazo[1,2-a]Pyridine

(184) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (400 mg), 6-bromo-imidazo[1,2-a]pyridine (291 mg), PdCl<sub>2</sub>(dppf) DCM (110 mg), K<sub>3</sub>PO<sub>4</sub> (570 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 100° C. for 3 hours. AcOEt and water were added to the reaction solution and the mixture was filtered through Celite. The organic layer was washed with water and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (DCM/AcOEt) to obtain the object compound (318 mg).

#### Example 123

##### Synthesis of 6-(2-Phenoxypyrimidin-5-Yl) Imidazo[1,2-b]Pyridazine

(185) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (400 mg), 6-chloro-imidazo[1,2-b]pyridazine (227 mg), PdCl<sub>2</sub>(dppf) DCM (110 mg),

K.sub.3PO.sub.4 (570 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 95° C. for 3 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (329 mg).

#### Example 137

##### Synthesis of 6-(2-Phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-5-yl)-1H-Pyrrolo[3,2-b]Pyridine

(186) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (400 mg), 6-bromo-1-(triisopropylsilyl)-1H-pyrrolo[3,2-b]pyridine (522 mg), PdCl.sub.2 (dppf) DCM (110 mg), K.sub.3PO.sub.4 (570 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 90° C. for 3 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was dissolved in THF (5 mL), IN-TBAF (1.34 mL) was added thereto, the mixture was stirred at room temperature for 1 hour, and the reaction solution was concentrated under a reduced pressure. The residue was purified through basic silica gel column chromatography (DCM/AcOEt) to obtain the object compound (325 mg).

#### Example 139

##### Synthesis of 4-(2-Phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-5-yl)-1,8-Naphthyridine

(187) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (300 mg), 4-chloro-[1,8]naphthyridine (199 mg), K.sub.3PO.sub.4 (427 mg), PdCl.sub.2 (dppf) DCM (6.56 mg), 1,4-dioxane (4 mL), and water (2 mL) was heated to reflux under a nitrogen atmosphere for 3 hours. Water was added to the reaction solution, the product was extracted with AcOEt. The organic layer was dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (MeOH/DCM), and the obtained solid was recrystallized from AcOEt to obtain the object compound (167 mg).

#### Example 163

##### Synthesis of 6-(2-(3-Chlorophenoxy)Pyrimidin-5-yl) Imidazo[1,2-a]Pyridine

(188) A mixture containing 6-(2-(dodecylsulfonyl)pyrimidin-5-yl) imidazo[1,2-a]pyridine (300 mg), 1-chloro-3-hydroxybenzene (0.089 mL), K.sub.2CO.sub.3 (193 mg), and DMF (3 mL) was stirred at 80° C. for 5 hours. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic column chromatography (DCM/AcOEt) to obtain the object compound (194 mg).

#### Example 172

##### Synthesis of 5-(2-Phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-5-yl)-1H-Pyrrolo[3,2-b]Pyridin-2 (3H)-One

(189) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (560 mg), 5-bromo-1H,2H,3H-pyrrolo[3,2-b]pyridin-2-one (200 mg), PdCl.sub.2 (dppf) DCM (38.3 mg), K.sub.3PO.sub.4 (399 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 90° C. for 5 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water, dried with anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (DCM/AcOEt) to obtain the object compound (98 mg).

#### Example 173

##### Synthesis of 6-(2-Phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-5-yl)-[1,2,3]Triazolo[1,5-a]Pyridine

(190) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (330 mg), 6-bromo-[1,2,3]triazolo[1,5-a]pyridine (241 mg), PdCl.sub.2 (dppf) DCM (45.2 mg), K.sub.3PO.sub.4 (470 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred at 90° C. for 5 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The filtrate was separated, and the organic layer was washed with water, dried with

anhydrous sodium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (DCM/AcOEt) to obtain the object compound (250 mg).

#### Example 198

Synthesis of 5-Methyl-6-(2-Phenoxy-5-yl) Imidazo[1,2-a]Pyridine Hydrochloride (191) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (330 mg), 6-bromo-5-methyl-imidazo[1,2-a]pyridine (257 mg), PdCl<sub>2</sub>.sub.2 (dppf) DCM (45.2 mg), K<sub>2</sub>CO<sub>3</sub> (470 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred at 90° C. for 5 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (DCM/AcOEt). The obtained oily material was dissolved in EtOH, a 3 mL IN-HCl EtOH solution was added thereto, the mixture was stirred, and the reaction solution was then concentrated. The precipitated crystals were recrystallized from EtOH/AcOEt to obtain the object compound (349 mg).

#### Example 220

Synthesis of 1-(2-Phenoxy-5-yl)Tetrahydropyrimidin-2 (1H)-One (192) 60% NaH (0.148 g) was added to a DMF (12 mL) solution containing 1-(3-chloropropyl)-3-(2-phenoxy-5-yl) urea (1.25 g) while ice-cooling and stirring, and the mixture was stirred at room temperature for 2 days. Water was added to the residue, and the product was extracted with AcOEt. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The precipitated crystals were washed with EtOH to obtain the object compound (181 mg).

#### Example 221

Synthesis of 1-(2-(3-Fluorophenoxy)Pyrimidin-5-yl)Tetrahydropyrimidin-2 (1H)-One (193) 2-(3-Fluorophenoxy)pyrimidin-5-amine (1.00 g) was dissolved in THF (10 mL) and DMF (10 mL), and 3-chloropropyl isocyanate (0.800 mL) was added thereto, and the mixture was stirred at 50° C. for 3 hours. Water was added to the reaction solution, and the precipitated crystals were then collected by filtration to obtain an intermediate (1.41 g). The intermediate was dissolved in DMF (14 mL), 60% NaH (0.214 g) was added thereto under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Ice water was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (AcOEt/MeOH), and the obtained solid was washed with EtOH to obtain the object compound (460 mg).

#### Example 223

Synthesis of 2-Phenoxy-5-(Piperidine-1-yl)Pyrimidine

(194) A mixture containing 5-bromo-2-phenoxy-5-methylpyrimidine (500 mg), piperidine (0.256 mL), Pd(OAc)<sub>2</sub> (447 mg), tBu<sub>3</sub>PMg.HBF<sub>4</sub> (578 mg), NaOtBu (191 mg), and toluene (10 mL) was stirred under a nitrogen atmosphere at 100° C. for 1 hour. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel chromatography (Hexane/AcOEt) to obtain the object compound (53 mg).

#### Example 226

Synthesis of 1-(2-Phenoxy-5-yl) Piperidin-4-Ol

(195) TBAF (0.56 mL) was added to THF (6 mL) containing 2-phenoxy-5-(4-(triisopropylsilyloxy) piperidin-1-yl)pyrimidine (240 mg), and the mixture was stirred at room temperature for 30 minutes. The reaction solution was concentrated, the residue was purified through silica gel column chromatography (Hexane/AcOEt), and crystallized from Hexane/AcOEt to obtain the object compound (110 mg).

#### Example 229

##### Synthesis of 4-(2-Phenoxy pyrimidin-5-Yl) Morpholin-3-One

(196) A mixture containing 5-iodo-2-phenoxy pyrimidine (500 mg), 3-ketomorpholine (254 mg), copper iodide (I) (31.9 mg), K.sub.3PO.sub.4 (712 mg), (1R,2R)-N,N-dimethyl-1,2-cyclohexanediamine (0.053 mL), and 1,4-dioxane (6 mL) was stirred at 90° C. for 4 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (368 mg).

#### Example 239

##### Synthesis of 4-(2-Phenoxy pyrimidin-5-Yl) Aniline

(197) A mixture containing 5-(4-nitrophenyl)-2-phenoxy pyrimidine (3.8 g), 10% Pd/C (0.4 g), and EtOH (80 mL) was stirred under a hydrogen atmosphere at room temperature for 1 hour. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt) to obtain a desired white solid product (2.5 g).

#### Example 240

##### Synthesis of 6-(2-Phenoxy pyrimidin-5-Yl) Benzo[d]Thiazol-2-Amine

(198) An acetic acid (2 mL) solution containing bromine (0.140 mL) was added to an acetic acid (6 mL) solution containing 4-(2-phenoxy pyrimidin-5-yl) aniline (600 mg) and ammonium thiocyanate (382 mg) while ice-cooling and stirring. After 1 hour, the reaction solution was poured into ice water, a 28% aqueous ammonia solution was added until the reaction system became basic, and the product was then extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (542 mg).

#### Example 257

##### Synthesis of 5-(2-Phenoxy pyrimidin-5-Yl)-1H-Benzo[d]Imidazole Oxalate

(199) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (400 mg), 5-bromo-1H-benzo[d]imidazole (291 mg), PdCl.sub.2 (dppf) DCM (110 mg), K.sub.3PO.sub.4 (570 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 95° C. for 3 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt). The obtained oily material was dissolved in ethanol, and an ethanol solution (1 mL) containing oxalic acid (80 mg) was added thereto. The precipitate was collected by filtration and dried to obtain the object compound (250 mg).

#### Example 262

##### Synthesis of 5-(2-Phenoxy pyrimidin-5-Yl)-1H-Indole

(200) A mixture containing 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (400 mg), 5-bromo-1-(triisopropylsilyl)-1H-indole (520 mg), PdCl.sub.2 (dppf) DCM (110 mg), K.sub.3PO.sub.4 (570 mg), 1,4-dioxane (4 mL), and water (2 mL) was stirred under a nitrogen atmosphere at 80° C. for 3 hours. AcOEt and water were added to the reaction solution, and the mixture was then filtered through Celite. The filtrate was separated, and the organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was dissolved in THF (10 mL), TBAF (1.342 mL) was added thereto, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated and then purified through silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (319 mg).

#### Example 302

##### Synthesis of 1-(4-(3-Fluorophenoxy)Phenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(201) A mixture containing 4-(3-fluorophenoxy) aniline (5.00 g), acrylic acid (2.53 mL), and toluene (40 mL) was stirred at 80° C. overnight. The reaction solution was concentrated, and urea

(4.43 g) and AcOH (20 mL) were added thereto, and the mixture was heated to reflux for 3 hours. Water was added thereto, and the precipitate was collected by filtration. The precipitate was purified through silica gel column chromatography (DCM/MeOH) to obtain the object compound (2.33 g).

#### Example 305

##### Synthesis of 1-(4-(3-Fluorobenzyl)Phenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(202) A mixture containing m-fluorobenzyl chloride (0.11 mL), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)dihydropyrimidine-2,4 (1H,3H)-dione (0.25 g), K.sub.3PO.sub.4 (0.252 g), PdCl.sub.2 (dppf) DCM (6.46 mg), DME (6.6 mL), and water (3.3 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (30 mg).

#### Example 308

##### Synthesis of 1-(4-(3-Fluorophenoxy)Phenyl)-3-Methyldihydropyrimidine-2,4 (1H,3H)-Dione

(203) 60% NaH (32.0 mg) was added to a DMF (5 mL) solution containing 1-(4-(3-Fluorophenoxy)phenyl)dihydropyrimidine-2,4 (1H,3H)-dione (200 mg) while stirring at 0° C. and stirring was performed for 30 minutes. Methyl iodide (0.046 mL) was added thereto while stirring at 0° C. and then stirring was performed at room temperature overnight. The reaction solution was poured into ice water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through basic silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (50 mg).

#### Example 314

##### Synthesis of 1-{4-[3-(Difluoromethoxy) Phenoxy]Phenyl}Dihydropyrimidine-2,4 (1H,3H)-Dione

(204) A mixture containing 1-[4-(3-hydroxy)phenyl]dihydropyrimidine-2,4 (1H,3H)-dione (337 mg), sodium chlorodifluoroacetate (344 mg), K.sub.2CO.sub.3 (234 mg) and DMF (1.7 mL) was stirred at 90° C. for 4 hours. Sodium chlorodifluoroacetate (344 mg) was added thereto and the mixture was additionally stirred for 2 hours. Hydrochloric acid was added to the reaction solution, and the product was then extracted with AcOEt. Washing with water, a NaOH aqueous solution, and water was performed, drying with anhydrous magnesium sulfate was performed, and concentration was then performed. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and crystallized by adding EtOH, and washed with EtOH to obtain the object compound (79 mg).

#### Example 321

##### Synthesis of 1-[4-(6-Fluoropyridin-2-Yloxy)Phenyl]Dihydropyrimidine-2,4 (1H,3H)-Dione

(205) A mixture containing 1-(4-hydroxyphenyl)dihydropyrimidine-2,4 (1H,3H)-dione (412 mg), 2,6-difluoropyridine (0.218 mL), K.sub.2CO.sub.3 (553 mg), and DMSO (2 mL) was stirred at 100° C. for 2 hours. Water (10 mL) was added to the reaction solution and the precipitated solid was collected by filtration. The solid was purified through silica gel column chromatography (DCM/MeOH), and the obtained solid was washed with EtOH to obtain the object compound (244 mg).

#### Example 322

##### Synthesis of 1-(4-Phenoxyphenyl)Pyrimidine-2,4 (1H,3H)-Dione

(206) A mixture containing 4-phenoxyphenylboronic acid (1.27 g), uracil (0.798 g), N,N,N',N'-tetramethylethylenediamine (0.896 mL), copper acetate (II) (0.539 g), MeOH (40 mL), and water (10 mL) was stirred at room temperature overnight. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and dried with anhydrous magnesium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (160 mg).

#### Example 327

##### Synthesis of 1-((1,1'-Biphenyl)-4-Yl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(207) A mixture containing monobromobenzene (0.158 mL), 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]dihydropyrimidine-2,4 (1H,3H)-dione (316 mg), Pd(Ph.sub.3P).sub.4 (57.8 mg), Na.sub.2CO.sub.3 (212 mg), DME (5 mL), and water (1 mL) was heated to reflux under a nitrogen atmosphere for 12 hours. AcOEt and anhydrous magnesium sulfate were added to the reaction solution, and the mixture was then filtered through Celite. The filtrate was concentrated, the residue was purified through silica gel chromatography (DCM/MeOH), and the obtained solid was washed with EtOH to obtain the object compound (35 mg).

#### Example 328

##### Synthesis of 6-Methyl-1-(4-Phenoxyphenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(208) A mixture containing 4-phenoxyaniline (0.50 g), toluene (5 mL), and crotonic acid (0.34 mL) was heated to reflux for 13 hours. Crotonic acid (0.34 mL) was added thereto, and additionally the mixture was heated to reflux for 6 hours. The reaction solution was concentrated, acetic acid (5 mL) and urea (0.324 g) were added thereto, and the mixture was heated to reflux for 17 hours. Concentrated hydrochloric acid (0.23 mL) was added to the reaction solution and heated to reflux for 30 minutes. Water was added to the reaction solution, and the product was then extracted with AcOEt. Washing with water, a saturated NaHCO.sub.3 aqueous solution, and brine was performed, and drying with anhydrous magnesium sulfate was performed, and concentration was then performed. The residue was crystallized by adding EtOH (3 mL) and IPE (3 mL). The solid was collected by filtration, and washed with IPE to obtain the object compound (272 mg).

#### Example 337

##### Synthesis of 6,6-Dimethyl-1-(4-Phenoxyphenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(209) A mixture containing 4-phenoxyaniline (1.0 g) and 3,3-dimethylacrylic acid (2.70 g) was stirred at 70° C. to 80° C. for 75 hours. Urea (0.648 g) and AcOH (6 mL) were added to the reaction solution and heated to reflux for 5 hours. Water (20 mL) was added to the reaction solution, and a saturated NaHCO.sub.3 aqueous solution was then added thereto for neutralization. Extraction in AcOEt was performed, then the extract was washed with a saturated NaCl aqueous solution, dried with anhydrous magnesium sulfate, and concentrated. The residue was purified through silica gel column chromatography (Hexane/AcOEt), and the obtained solid was washed with EtOH to obtain the object compound (103 mg).

#### Example 343

##### Synthesis of 6-Ethyl-1-(4-Phenoxyphenyl)Dihydropyrimidine-2,4 (1H,3H)-Dione

(210) A mixture containing 4-phenoxyaniline (0.50 g) and trans-2-pentenoic acid (1.37 mL) was stirred at 120° C. for 5 hours. AcOH (5 mL) and urea (0.324 g) were added to the reaction solution and heated to reflux for 3 hours. Water and AcOEt were added to the reaction solution and separated. The organic layer was washed with a saturated NaHCO.sub.3 aqueous solution and brine, and dried with anhydrous magnesium sulfate, and then concentrated. The residue was purified through silica gel column chromatography . . . (DCM/MeOH) and crystallized by adding EtOH (2 mL). The solid was collected by filtration, and washed with EtOH and IPE to obtain the object compound (204 mg).

#### Example 344

##### Synthesis of 1-[4-(3,5-Difluoromethoxy)Phenyl]Dihydropyrimidine-2,4 (1H,3H)-Dione

(211) A mixture containing 1-(4-hydroxyphenyl)dihydropyrimidine-2,4 (1H,3H)-dione (330 mg), 1,3,5-trifluorobenzene (0.199 mL), K.sub.2CO.sub.3 (442 mg), and DMSO (2 mL) was stirred at 100° C. for 3.5 hours. 1,3,5-trifluorobenzene (0.199 mL) was added thereto, and additionally the mixture was stirred for 1.5 hours. Water (15 mL) was added to the reaction solution, and the precipitated solid was then collected by filtration, and washed with water and EtOH to obtain the object compound (35 mg).

#### Example 346



#### Synthesis of 1-(6-Phenoxypyridazin-3-Yl)Pyrimidine-2,4 (1H,3H)-Dione











(212) A mixture containing phenol (1.017 mL), 1-(6-chloropyridazine-3-yl)pyrimidine-2,4 (1H,3H)-dione (2.00 g), Cs.sub.2CO.sub.3 (4.35 g), and DMSO (20 mL) was stirred at 130° C. overnight. A citric acid aqueous solution was added to the reaction solution, and the product was then extracted with AcOEt. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate, and concentrated. The residue was washed with EtOH to obtain the object compound (588 mg).







#### Example 347

#### Synthesis of 1-(6-Phenoxypyridazin-3-Yl)Dihydropyrimidine-2,4 (1H,3H)-Dione




(213) 1-(6-Phenoxypyridazin-3-yl)pyrimidine-2,4 (1H,3H)-dione (577 mg) was dissolved in DMF (10 mL), and 50% water-containing 10% Pd/C (500 mg) was added, and the mixture was stirred under a hydrogen atmosphere at 50° C. for 6 hours. The reaction solution was filtered through Celite, and the filtrate was concentrated. The residue was purified through medium pressure column chromatography (DCM/AcOEt), and the obtained solid was washed with EtOH to obtain the object compound (122 mg).











(214) The compounds of Examples 2, 3, 5, 8 to 10, 12 to 23, 25 to 29, 31 to 35, 37, 39 to 59, 61, 62, 64 to 68, 70, 71, 73 to 83, 85 to 87, 89, 90, 93, 95 to 105, 107 to 113, 115 to 117, 120 to 122, 124 to 136, 138, 140 to 162, 164 to 171, 174 to 197, 199 to 219, 222, 224, 225, 227, 228, 230 to 238, 241 to 256, 258 to 261, 263 to 301, 303, 304, 306, 307, 309 to 313, 315 to 320, 323 to 326, 329 to 336, 338 to 342, 345 and 348 to 350 were manufactured in the same manner as in Examples 1, 4, 6, 7, 11, 24, 30, 36, 38, 60, 63, 69, 72, 84, 88, 91, 92, 94, 106, 114, 118, 119, 123, 137, 139, 163, 172, 173, 198, 220, 221, 223, 226, 229, 239, 240, 257, 262, 302, 305, 308, 314, 321, 322, 327, 328, 337, 343, 344, 346 and 347. Structural formulae and physicochemical data of the compounds of Examples 1 to 350 are shown in Tables 2-1 to 2-37.











(215) TABLE-US-00013 TABLE 2-1 EX STR Prop DATA 1  embedded image 1 NMR2; 4.20(3H, s), 7.11(1H, d, J = 9.2 Hz), 7.20- 7.34(3H, m), 7.42-7.52(2H, m), 7.73(1H, d, J = 9.2 Hz), 9.16(2H, s). 2  embedded image 1 NMR2; 4.20(3H, s), 7.11(1H, d, J = 9.2 Hz), 7.20- 7.34(3H, m), 7.42-7.52(2H, m), 7.73(1H, d, J = 9.2 Hz), 9.16(2H, s). 3  embedded image 1 NMR2; 4.21(3H, s), 7.11(1H, d, J = 9.2 Hz), 7.18- 7.37(4H, m), 7.73(1H, d, J = 9.2 Hz), 9.16(2H, s). 4  embedded image 4 NMR2; 4.21(3H, s), 6.96-7.09(3H, m), 7.12(1H, d, J = 9.2 Hz), 7.37-7.47(1H, m), 7.74(1H, d, J = 9.2 Hz), 9.18(2H, s). 5  embedded image 1 NMR2; 4.21(3H, s), 7.08-7.25(5H, m), 7.73(1H, d, J = 9.2 Hz), 9.18(2H, s). 6  embedded image 6 NMR2; 3.99(3H, s), 6.87(1H, dd, J = 0.8, 8.6 Hz), 7.19-7.33(3H, m), 7.41-7.51(2H, m), 7.72(1H, dd, J = 2.6, 8.6 Hz), 8.32(1H, dd, J = 0.8, 2.5 Hz), 8.70(2H, s) 7  embedded image 7 NMR2; 7.20-7.34(3H, m), 7.39-7.52(3H, m), 7.79-7.87(1H, m), 8.69(1H, dd, J = 1.6, 4.8 Hz), 8.77(2H, s), 8.80(1H, dd, J = 0.9, 2.4 Hz). 8 0  embedded image 7 NMR2; 2.63(3H, s), 7.20-7.34(4H, m), 7.43- 7.52(2H, m), 7.72(1H, dd, J = 2.5, 8.0 Hz), 8.67(1H, dd, J = 0.9, 2.5 Hz), 8.74(2H, s). 9  embedded image 1 NMR2; 7.20-7.34(3H, m), 7.42-7.52(4H, m), 8.70-8.77(2H, m), 8.82(2H, s). 10  embedded image 1 NMR2; 7.20-7.28(2H, m), 7.28-7.36(1H, m), 7.42-7.52(2H, m), 7.67(1H, dd, J = 5.3, 1.5 Hz), 8.83(1H, d, J = 5.3 Hz), 8.25(2H, s), 9.29(1H, d, J = 1.4 Hz).






(216) TABLE-US-00014 TABLE 2-2 EX STR Prop DATA 11  embedded image 11 NMR2; 7.19-7.36(3H, m), 7.37-7.53(4H, m), 8.22-8.31(1H, m), 8.38-8.44(1H, m), 8.74(2H, s). 12  embedded image 1 NMR2; 4.21(3H, s), 7.12(1H, d, J = 9.2 Hz), 7.41- 7.49(1H, m), 7.50-7.64(3H, m), 7.75(1H, d, J = 9.2 Hz), 9.18(2H, s). 13  embedded image 1 NMR2; 2.80(3H, s), 7.41-7.50(2H, m), 7.50- 7.64(3H, m), 7.73(1H, d, J = 8.7 Hz), 9.23(2H, s). 14  embedded image 7 NMR2; 7.41-7.49(2H, m), 7.50-7.64(3H, m), 7.81-7.89(1H, m), 8.70(1H, dd, J = 1.8, 4.9 Hz), 8.78(2H, s), 8.82(1H, dd, J = 0.9, 2.5 Hz). 15  embedded image 7 NMR2; 2.63(3H, s), 7.26-7.34(1H, m), 7.40- 7.48(1H, m), 7.60-7.63(3H, m), 7.73(1H, dd, J = 2.4, 8.0 Hz), 8.55-8.71(1H, m), 8.75(2H, s). 16  embedded image 7 NMR2; 3.99(3H, s), 6.88(1H, dd, J = 0.8, 8.5 Hz), 7.40-7.48(1H, m), 7.49-7.63(3H, m), 7.73(1H, dd, J = 2.6, 8.6 Hz), 8.34(1H, dd, J = 0.8, 2.5 Hz),


















8.71(2H, s). 17  embedded image 1 NMR2; 2.80(3H, s), 6.73-6.80(1H, m), 6.81- 6.88(2H, m), 7.47(1H, d, J = 8.8 Hz), 7.74(1H, d, J = 8.7 Hz), 9.25(2H, s). 18 0  embedded image 1 NMR2; 6.73-6.80(1H, m), 6.80-6.87(2H, m), 7.46(1H, ddd, J = 0.8 Hz, 4.9 Hz, 7.9 Hz), 7.85(1H, ddd, J = 1.7 Hz, 2.4 Hz, 7.9 Hz), 8.71(1H, dd, J = 1.6 Hz, 4.8 Hz), 8.79(2H, s), 8.82(1H, dd, J = 0.8 Hz, 2.3 Hz). 19  embedded image 1 NMR2; 4.21(3H, s), 6.72-6.80(1H, m), 6.80- 6.87(2H, m), 7.23(1H, d, J = 9.2 Hz), 7.75(1H, d, J = 9.2 Hz), 9.19(2H, s).











(217) TABLE-US-00015 TABLE 2-3 EX STR Prop DATA 20  embedded image 1 NMR2; 4.85(2H, s), 6.86(1H, d, J = 9.2 Hz), 7.08- 7.16(2H, m), 7.16-7.25(2H, m), 7.57(1H, d, J = 9.2 Hz), 9.11(2H, s). 21  embedded image 1 NMR2; 2.80(3H, s), 6.96-7.10(3H, m), 7.37- 7.49(2H, m), 7.73(1H, d, J = 8.7 Hz), 9.23(2H, s). 22  embedded image 1 NMR2; 2.65(3H, s), 7.17-7.35(5H, m), 7.42- 7.52(2H, m), 8.81(1H, dd, J = 0.8, 5.2 Hz), 8.79(2H, s). 23  embedded image 1 NMR2; 3.99(3H, s), 6.89(1H, dd, J = 0.8, 1.6 Hz), 7.03(1H, dd, J = 1.6, 5.3 Hz), 7.17-7.34 (3H, m), 7.40-7.52(2H, m), 8.24-8.30(1H, m), 8.78(2H, s). 24  embedded image 24 NMR2; 4.86(2H, s), 6.87(1H, d, J = 9.2 Hz), 6.95- 7.09(3H, m), 7.41(1H, td, J = 8.7, 6.6 Hz), 7.58(1H, d, J = 9.5 Hz), 9.12(2H, s). 25  embedded image 1 NMR2; 2.79(3H, s), 7.18-7.39(4H, m), 7.45(1H, d, J = 8.7 Hz), 7.72(1H, d, J = 8.7 Hz), 9.22(2H, s). 26  embedded image 1 NMR2; 4.87(2H, s), 6.86(1H, d, J = 9.2 Hz), 7.17- 7.37(4H, m), 7.57(1H, d, J = 9.2 Hz), 9.11(2H, s). 27  embedded image 1 NMR2; 7.20-7.28(2H, m), 7.31(1H, ddt, J = 7.9, 7.0, 1.1 Hz), 7.43-7.53(2H, m), 7.83(1H, dd, J = 8.2, 0.9 Hz), 8.02(1H, ddd, J = 8.1, 2.3, 0.7 Hz), 8.80(2H, s), 8.91(1H, d, J = 2.2 Hz). 28 0  embedded image 7 NMR2; 2.40(3H, d, J = 0.7 Hz), 2.63(3H, s), 6.97- 7.15(3H, m), 7.25-7.38(2H, m), 7.72(1H, dd, J = 2.4, 8.0 Hz), 8.67(1H, dd, J = 0.9, 2.5 Hz), 8.74(2H, s). 29  embedded image 7 NMR2; 2.40(3H, s), 3.99(3H, s), 6.57(1H, dd, J = 0.8, 8.8 Hz), 5.99-7.08(2H, m), 7.06-7.13(1H, m), 7.34(1H, t, J = 7.8 Hz), 7.71(1H, dd, J = 2.6, 8.6 Hz), 8.32(1H, dd, J = 0.8, 2.6 Hz), 8.70(2H, s).





(218) TABLE-US-00016 TABLE 2-4 EX STR Prop DATA 30  embedded image 1 NMR2; 4.86(2H, s), 6.86(1H, d, J = 9.2 Hz), 7.20- 7.33(3H, m), 7.41-7.51(2H, m), 7.57(1H, d, J = 9.2 Hz), 9.11(2H, s). 31  embedded image 1 NMR2; 7.20-7.28(2H, m), 7.28-7.37 (1H, m), 7.43-7.53(2H, m), 7.83(1H, dd, J = 2.5, 5.4 Hz), 8.87(2H, s), 9.32(1H, dd, J = 1.2, 5.4 Hz), 9.45(1H, dd, J = 1.2, 2.5 Hz). 32  embedded image 1 NMR2; 6.96-7.09(3H, m), 7.38-7.47(1H, m), 7.64(1H, dd, J = 2.5, 5.4 Hz), 8.88(2H, s), 9.33(1H, dd, J = 1.2, 5.4 Hz), 9.45(1H, dd, J = 1.2, 2.5 Hz). 33  embedded image 1 NMR2; 7.09(1H, ddd, J = 8.5, 3.1, 0.7 Hz), 7.19- 7.28(2H, m), 7.26-7.35(1H, m), 7.42-7.52(2H, m), 7.88-7.98(1H, m), 8.36-8.42(1H, m), 8.73(2H, s). 34  embedded image 1 NMR2; 2.54(3H, s), 7.21-7.34(4H, m), 7.42- 7.55(3H, m), 8.55(2H, s), 5.58(1H, dd, J = 4.9, 1.8 Hz). 35  embedded image 7 NMR2; 2.41(3H, d, J = 0.8 Hz), 6.99-7.08(2H, m), 7.11(1H, tdd, J = 0.8, 1.6, 7.5 Hz), 7.35(1H, t, J = 7.7 Hz), 7.44(1H, ddd, J = 0.9, 4.9, 7.9 Hz), 7.79- 7.87(1H, m), 8.59(1H, dd, J = 1.6, 4.8 Hz), 8.76(2H, s), 8.80(1H, dd, J = 0.9, 2.4 Hz). 36  embedded image 36 NMR2; 4.59(2H, s), 5.51(1H, dd, J = 8.5, 0.9 Hz), 7.19-7.32(3H, m), 7.40-7.50(2H, m), 7.58(1H, dd, J = 8.5, 2.5 Hz), 8.24(1H, dd, J = 2.5, 0.8 Hz), 8.67(2H, s). 37  embedded image 1 NMR2; 6.70 (1H, t, J = 55.3 Hz), 7.23-7.33 (3H, m), 7.46-7.50 (2H, m), 7.78(1H, d, J = 8.12 Hz), 7.98-8.00(1H, m), 8.79(2H, s), 8.83(1H, m). 38 0  embedded image 38 NMR2; 7.26(2H, dd, J = 8.6, 1.3 Hz), 7.32(1H, t, J = 7.5 Hz), 7.44-7.54(2H, m), 7.94(1H, d, J = 8.9 Hz), 8.01(1H, d, J = 8.9 Hz), 9.31(2H, s). 39  embedded image 1 NMR2; 4.55(2H, s), 6.86(1H, d, J = 9.2 Hz), 6.99- 7.11(2H, m), 7.16-7.27(1H, m), 7.88(1H, d, J = 9.2 Hz), 9.12(2H, s).







(219) TABLE-US-00017 TABLE 2-5 EX STR Prop DATA 40  embedded image 1 NMR2; 4.87(2H, s), 6.87(1H, d, J = 9.2 Hz), 7.41- 7.48(1H, m), 7.49-7.62(4H, m), 9.13(2H, s). 41  embedded image 1 NMR2; 4.87(2H, s), 6.75(1H, tt, J = 8.9, 2.3 Hz), 6.78-6.91(3H, m), 7.59(1H, d, J = 9.2 Hz), 9.14(2H, s). 42  embedded image 1 NMR2; 4.87(2H, s), 6.87(1H, d, J = 9.2 Hz), 7.11- 7.24(3H, m), 7.42-7.52(1H, m), 7.59(1H, d, J = 9.2 Hz), 9.13(2H, s). 43  embedded image 1 NMR2; 4.61(2H, s), 6.62(1H, dd, J = 8.5, 0.8 Hz), 6.94-7.08(3H, m), 7.40(1H, td, J = 8.6, 6.5 Hz), 7.55-7.63(1H, m), 8.25(1H, d, J = 2.4 Hz), 8.68(2H, s). 44  embedded image 1 NMR2; 4.60(2H,










s), 6.61(1H, dd, J = 8.5, 0.8 Hz), 7.07-7.15(2H, m), 7.15-7.25(2H, m), 7.58(1H, dd, J = 8.5, 2.5 Hz), 8.24(1H, dd, J = 2.5, 0.8 Hz), 8.67(2H, s). 45  embedded image 1 NMR2; 4.60(2H, s), 6.61(1H, dd, J = 8.5, 0.8 Hz), 7.17-7.36(4H, m), 7.59(1H, dd, J = 8.5, 2.5 Hz), 8.25(1H, dd, J = 2.5, 0.8 Hz), 8.67(2H, s). 46  embedded image 1 NMR2; 6.98-7.11(3H, m), 7.39-7.49(1H, m), 7.95(1H, d, J = 8.9 Hz), 8.03(1H, dd, J = 8.9, 0.8 Hz), 9.33(2H, s). 47  embedded image 1 NMR2; 2.55(3H, s), 6.96-7.07(2H, m), 7.04- 7.11(1H, m), 7.26(1H, d, J = 12.6 Hz), 7.37-7.48 (1H, m), 7.52(1H, dd, J = 7.7, 1.8 Hz), 8.56(2H, s), 8.59-8.60(1H, m). 48 0  embedded image 1 NMR2; 4.61(2H, s), 6.62(1H, dd, J = 8.5, 0.8 Hz), 7.10-7.23(3H, m), 7.42-7.51(1H, m), 7.60(1H, dd, J = 8.5, 2.5 Hz), 8.26(1H, dd, J = 2.5, 0.8 Hz), 8.69(2H, s). 49  embedded image 1 NMR2; 2.54(3H, s), 7.09-7.20(2H, m), 7.18- 7.34(3H, m) 7.51(1H, dd, J = 7.7, 1.8 Hz), 8.58(2H, s), 8.59(1H, dd, J = 4.9, 1.8 Hz).











(220) TABLE-US-00018 TABLE 2-6 EX STR Prop DATA 50  embedded image 1 NMR2; 4.62(2H, s), 6.62(1H, dd, J = 8.5, 0.9 Hz), 7.39-7.47(1H, m), 7.46-7.64(4H, m), 8.26(1H, dd, J = 2.5, 0.9 Hz), 8.68(2H, s). 51  embedded image 1 NMR2; 7.19-7.27(2H, m), 7.26-7.36 (1H, m), 7.42-7.52(3H, m), 7.80(1H, dd, J = 8.3, 2.6 Hz), 8.57(1H, dd, J = 2.6, 0.8 Hz), 8.74(2H, s). 52  embedded image 1 NMR2; 4.61(2H, s), 6.61(1H, dd, J = 8.5, 0.8 Hz), 6.98-7.10(2H, m), 7.16-7.26(1H, m), 7.59(1H, dd, J = 8.5, 2.5 Hz), 8.26(1H, dd, J = 2.5, 0.9 Hz), 8.67(2H, s). 53  embedded image 1 NMR2; 4.63(2H, s), 6.62(1H, dd, J = 8.5, 0.8 Hz), 6.74(1H, tt, J = 8.9, 2.3 Hz), 6.76-6.87(2H, m), 7.60(1H, dd, J = 8.5, 2.5 Hz), 8.26(1H, dd, J = 2.6, 0.9 Hz), 8.70(2H, s). 54  embedded image 1 NMR2; 2.55(3H, s), 7.00-7.12(2H, m), 7.18- 7.30(2H, m), 7.53(1H, dd, J = 7.7, 1.8 Hz), 8.56(2H, s), 8.59(1H, dd, J = 4.9, 1.8 Hz). 55  embedded image 1 NMR2; 4.59(2H, s), 6.61(1H, dd, J = 1.6, 0.8 Hz), 6.80(1H, dd, J = 5.3, 1.6 Hz), 7.19-7.27(2H, m), 7.25-7.34(1H, m), 7.42-7.52(2H, m), 8.17 (1H, dd, J = 5.4, 0.8 Hz), 8.75(2H, s). 56  embedded image 1 NMR2; 2.55(3H, s), 6.76(1H, tt, J = 8.9, 2.3 Hz), 6.80-6.91(2H, m), 7.25-7.34(1H, m), 7.52(1H, dd, J = 7.7, 1.8 Hz), 8.58(2H, s), 8.60(1H, dd, J = 4.9, 1.8 Hz). 57  embedded image 1 NMR2; 7.11-7.27(4H, m), 7.91-8.06(2H, m), 9.31(2H, s). 58 00  embedded image 1 NMR2; 3.87(2H, s), 7.07(1H, dd, J = 2.7, 1.9 Hz), 7.20-7.34(3H, m), 7.41-7.52(2H, m), 8.16(2H, dd, J = 10.9, 2.3 Hz), 8.72(2H, s). 59 01  embedded image 1 NMR2; 2.36(3H, s), 4.51(2H, s), 5.44(1H, dd, J = 8.3, 0.7 Hz), 7.21-7.33(4H, m), 7.41-7.51(2H, m), 8.49(2H, s).

(221) TABLE-US-00019 TABLE 2-7 EX STR Prop DATA 60 02  embedded image 60 NMR2; 7.19-7.36(4H, m), 7.35-7.46(2H, m), 8.26(1H, td, J = 1.8, 5.5 Hz), 8.39-8.45 (1H, m), 8.74(2H, s). 61 03  embedded image 60 NMR2; 6.95-7.08(3H, m), 7.36-7.48(3H, m), 8.27(1H, td, J = 1.7, 5.8 Hz), 8.39-8.45(1H, m), 8.75(2H, s). 62 04  embedded image 60 NMR2; 7.09-7.25(4H, m), 7.35-7.46(2H, m), 8.26(1H, td, J = 1.7, 5.8 Hz), 8.38-8.44(1H, m), 8.74(2H, s). 63 05  embedded image 63 NMR2; 4.21(3H, s), 6.98(1H, ddt, J = 9.2, 7.7, 3.4 Hz), 7.04-7.16(2H, m), 7.19(1H, td, J = 9.4, 5.0 Hz), 7.74(1H, d, J = 9.3 Hz), 9.17(2H, s). 64 06  embedded image 1 NMR2; 2.36(3H, s), 4.52(2H, s), 6.44(1H, dd, J = 8.3, 0.7 Hz), 7.19-7.34(4H, m), 7.41-7.51 (2H, m), 8.49(2H, s). 65 07  embedded image 63 NMR2; 4.21(3H, s), 6.90-7.05(2H, m), 7.12(1H, d, J = 9.2 Hz), 7.25-7.34(1H, m), 7.74(1H, d, J = 9.2 Hz), 9.16(2H, s). 66 08  embedded image 1 NMR2; 4.28(2H, s), 4.34(2H, s), 5.02(1H, d, J = 8.0 Hz), 7.13(1H, d, J = 8.0 Hz), 7.19-7.32(3H, m), 7.40-7.51(2H, m), 8.80(2H, s). 67 09  embedded image 1 NMR2; 7.15-7.26(3H, m), 7.45-7.55(1H, m), 7.96(1H, d, J = 6.8 Hz), 8.03(1H, dd, J = 8.9, 0.6 Hz), 9.33(2H, s). 68 0  embedded image 63 NMR2; 4.21(3H, s), 7.06-7.22(4H, m), 7.74(1H, d, J = 9.2 Hz), 9.17(2H, s). 69  embedded image 69 NMR2; 1.70(6H, s), 3.75(1H, s), 7.22-7.36(3H, m), 7.41-7.53(2H, m), 7.77-7.88(2H, m), 9.24(2H, s).

(222) TABLE-US-00020 TABLE 2-8 EX STR Prop DATA 70  embedded image 1 NMR2; 2.50(3H, s), 2.59(3H, s), 7.07-7.14(1H, m), 7.22-7.34(3H, m), 7.40(1H, d, J = 7.6 Hz), 7.42-7.52(2H, m), 8.53(2H, s). 71  embedded image 63 NMR1; 4.09(3H, s), 7.28(1H, ddd, J = 8.2, 2.3, 1.0 Hz), 7.34-7.44(2H, m), 7.44-7.55(2H, m), 8.26(1H, d, J = 9.3 Hz), 9.29(2H, s). 72  embedded image 72 NMR2; 3.15(1H, t, J = 5.5 Hz), 5.07(2H, d, J = 5.5 Hz), 7.21-7.36(3H, m), 7.43-7.53(2H, m), 7.63-7.70(1H, m), 7.84(1H, d, J = 8.8 Hz), 9.24(2H, s). 73  embedded image





























63 NMR2; 4.21(3H, s), 7.13(1H, d, J = 9.2 Hz), 7.47- 7.63(4H, m), 7.75(1H, d, J = 9.2 Hz), 9.18(2H, s). 74  embedded image 63 NMR2; 4.21(3H, s), 7.13(1H, d, J = 9.2 Hz), 7.42(1H, ddd, J = 8.3, 4.8, 0.7 Hz), 7.63(1H, ddd, J = 8.3, 2.7, 1.4 Hz), 7.75(1H, d, J = 9.2 Hz), 8.55(1H, dd, J = 4.7, 1.4 Hz), 8.62(1H, d, J = 2.7 Hz), 9.17(2H, s). 75  embedded image 1 NMR1; 6.81(2H, s), 7.19(1H, d, J = 5.1 Hz), 7.22- 7.34(3H, m), 7.42-7.52(2H, m), 8.36 (1H, d, J = 5.1 Hz), 9.22(2H, s.) 76  embedded image 1 NMR2; 2.55(2H, s), 7.23-7.31(1H, m), 7.47(1H, d, J = 7.5 Hz), 7.45-7.64(4H, m), 8.57(2H, s), 8.60(1H, dd, J = 4.9, 1.8 Hz). 77  embedded image 1 NMR2; 2.55(3H, s), 7.12-7.21(2H, m), 7.19-7.34 (2H, m), 7.44-7.66(2H, m), 8.87(2H, s), 8.59(1H, m). 78 0  embedded image 1 NMR1; 6.08(2H, s), 6.70(1H, dd, J = 1.7, 0.8 Hz), 6.84(1H, dd, J = 5.3, 1.6 Hz), 7.14(2H, tdt, J = 8.1, 2.0, 0.9 Hz), 7.25(1H, dt, J = 10.1, 2.3 Hz), 7.50(1H, td, J = 8.3, 6.8 Hz), 8.01(1H, dd, J = 5.3, 0.7 Hz), 8.94(2H, s). 79  embedded image 1 NMR1; 6.07(2H, s), 6.70(1H, dd, J = 1.7, 0.8 Hz), 6.83 (1H, dd, J = 6.3, 1.6 Hz), 7.24-7.36(4H, m), 8.00(1H, dd, J = 6.3, 0.8 Hz), 6.92(2H, s).

(223) TABLE-US-00021 TABLE 2-9 EX STR Prop DATA 80  embedded image 1 NMR1: 6.08(2H, s), 6.70(1H, dd, J = 1.7, 0.8 Hz), 6.84(1H, dd, J = 5.4, 1.6 Hz), 7.25-7.40(2H, m), 7.36-7.49(2H, m), 8.01(1H, dd, J = 5.4, 0.7 Hz), 8.94(2H, s). 81  embedded image 1 NMR2: 4.60(2H, s), 6.62(1H, dd, J = 1.6, 0.8 Hz), 6.81(1H, dd, J = 5.4, 1.0 Hz), 7.40-7.47(1H, m), 7.49-7.63(3H, m), 8.19(1H, dd, J = 5.4, 0.8 Hz), 8.78(2H, s). 82  embedded image 1 NMR1; 6.09(2H, s), 6.71(1H, dd, J = 1.6, 0.8 Hz), 6.85(1H, dd, J = 5.3, 1.7 Hz), 7.13-7.26(3H, m), 8.02(1H, dd, J = 5.4, 0.7 Hz), 8.97(2H, s) 83  embedded image 1 NMR1; 6.08(2H, s), 6.71(1H, s), 6.84(1H, dd, J = 5.3, 1.7 Hz), 7.33(2H, dddd, J = 13.9, 8.3, 2.3, 1.1 Hz), 7.40(1H, d, J = 2.8 Hz), 7.60(1H, t, J = 8.3 Hz), 8.01(1H, d, J = 5.2 Hz), 5.95(2H, s). 84  embedded image 84 NMR1; 6.23(2H, s), 6.54(1H, dd, J = 8.7, 0.8 Hz), 7.21(1H, ddt, J = 9.2, 6.0, 3.3 Hz), 7.41-7.54(2H, m), 7.76(1H, dd, J = 8.8, 2.6 Hz), 8.30(1H, dd, J = 2.6, 0.8 Hz), 8.90(2H, s). 85  embedded image 84 NMR1; 6.22(2H, s), 6.54(1H, dd, J = 8.7, 0.8 Hz), 7.13(1H, dddd, J = 9.2, 3.8, 2.8, 1.8 Hz), 7.46- 7.58(2H, m), 7.76(1H, dd, J = 8.6, 2.6 Hz), 8.30(1H, dd, J = 2.6, 0.8 Hz), 8.88(2H, s). 86  embedded image 84 NMR1; 6.23(2H, s), 6.54 (1H, dd, J = 8.7, 0.8 Hz), 7.12-7.23(1H, m), 7.43-7.55(2H, m), 7.75(1H, dd, J = 8.6, 2.6 Hz), 8.29(1H, dd, J = 2.5, 0.8 Hz), 8.88(2H, s). 87  embedded image 84 NMR1; 6.24(2H, s), 6.54(1H, dd, J = 8.6, 0.9 Hz), 7.24-7.37(2H, m), 7.33-7.47(1H, m), 7.76(1H, dd, J = 8.6, 2.6 Hz), 8.30(1H, dd, J = 2.6, 0.8 Hz), 8.90(2H, s). 88 0  embedded image 88 NMR1; 2.33(3H, s), 6.20(2H, s), 6.54(1H, dd, J = 8.6, 0.8 Hz), 6.95-7.06(2H, m), 7.07(1H, ddt, J = 7.6, 1.7, 0.9 Hz), 7.32(1H, t, J = 7.8 Hz), 7.74(1H, dd, J = 8.8, 2.6 Hz), 8.28(1H, dd, J = 2.6, 0.8 Hz), 8.85(2H, s).











(224) TABLE-US-00022 TABLE 2-10 EX STR Prop DATA 89  embedded image 84 NMR1; 6.23(2H, s), 6.54(1H, dd, J = 8.6, 0.8 Hz), 7.59-7.71(2H, m), 7.76(2H, ddd, J = 6.7, 3.7, 2.1 Hz), 7.85(1H, ddd, J = 2.1, 1.5, 0.7 Hz), 8.30(1H, dd, J = 2.5, 0.8 Hz), 8.90(2H, s). 90  embedded image 84 NMR1; 6.23(2H, s), 6.54(1H, dd, J = 8.7, 0.8 Hz), 7.52(1H, ddd, J = 8.4, 4.7, 0.7 Hz), 7.71-7.80(2H, m), 8.30(1H, dd, J = 2.6, 0.8 Hz), 8.45-8.57(2H, m), 8.89(2H, s). 91  embedded image 91 NMR2; 7.13(1H, d, J = 9.9 Hz), 7.18-7.27(2H, m), 7.26-7.35(1H, m), 7.42-7.52(2H, m), 7.67(1H, d, J = 9.9 Hz), 8.96(2H, s), 11.60(1H, s) 92  embedded image 92 NMR2; 2.62-2.71(2H, m), 2.9-3.00(2H, m), 7.16-7.25(2H, m), 7.24-7.34(1H, m), 7.40- 7.51(2H, m), 8.64(1H, s), 8.88(2H, s). 93  embedded image 7 NMR2; 6.95-7.08(3H, m), 7.15(1H, d, J = 9.9 Hz), 7.36-7.47(1H, m), 7.68(1H, d, J = 9.9 Hz), 8.98(2H, s), 11.81(1H, s). 94  embedded image 94 NMR2; 2.62-2.72(2H, m), 2.92-3.01(2H, m), 6.93-7.06(3H, m), 7.41(1H, dt, J = 6.5, 8.3 Hz), 8.61(1H, s), 8.89(2H, s). 95  embedded image 7 NMR2; 7.13(1H, d, J = 9.9 Hz), 7.18-7.36(4H, m), 7.66(1H, d, J = 9.9 Hz), 8.96(2H, s), 11.23(1H, s). 96  embedded image 92 NMR2; 2.62-2.71(2H, m), 2.91-3.00(2H, m), 7.16-7.34(4H, m), 8.63(1H, s), 8.88(2H, s). 97  embedded image 7 NMR2; 7.08-7.24(5H, m), 7.65(1H, d, J = 10.0 Hz), 8.95(2H, s), 10.68(1H, s). 98 0  embedded image 92 NMR2; 2.62-2.71(2H, m), 2.91-3.00(2H, m), 7.07-7.24(4H, m), 8.57 (1H, s), 8.87(2H, s)












(225) TABLE-US-00023 TABLE 2-11 EX STR Prop DATA 99  embedded image 7 NMR2;







7.15(1H, d, J = 9.9 Hz), 7.39-7.64(4H, m), 7.68(1H, d, J = 9.9 Hz), 6.98(2H, s), 11.71(1H, s). 100  embedded image 92 NMR2; 2.63-2.72(2H, m), 2.92-3.02(2H, m), 7.36-7.63(4H, m), 8.58(1H, s), 8.89(2H, s). 101  embedded image 7 NMR1; 7.07(1H, d, J = 9.9 Hz), 7.29-7.46(3H, m), 8.06(1H, d, J = 9.9 Hz), 9.12(2H, s), 13.39(1H, s). 102  embedded image 7 NMR1; 7.07(1H, d, J = 9.9 Hz), 7.14-7.25(3H, m), 8.07(1H, d, J = 9.9 Hz), 9.12(2H, s), 13.38(1H, s). 103  embedded image 7 NMR2; 6.75(1H, dd, J = 0.7, 9.4 Hz), 7.18-7.33(3H, m), 7.41-7.51(2H, m), 7.58(1H, d, J = 2.6 Hz), 7.67(1H, dd, J = 2.7, 9.6 Hz), 8.62(2H, s), 13.22(1H, s). 104  embedded image 92 NMR2; 2.67(2H, dd, J = 7.7 Hz, 8.8 Hz), 2.96(2H, dd, J = 7.7 Hz, 8.8 Hz), 6.99-7.08(2H, m), 7.18-7.26(1H, m), 8.62(1H, brs), 8.88(2Hs, s). 105  embedded image 92 NMR2; 2.68(2H, dd, J = 7.8 Hz, 8.9 Hz), 2.97(2H, dd, J = 7.7 Hz, 8.8 Hz), 6.72-6.84(3H, m), 8.66(1H, brs), 8.90(2H, s). 106  embedded image 2 NMR2; 2.40(3H, s), 6.75(1H, dd, J = 0.7, 9.4 Hz), 6.98-7.11(2H, m), 7.06-7.14(1H, m), 7.34(1H, t, J = 7.8 Hz), 7.56(1H, dd, J = 0.8, 2.7 Hz), 7.66(1H, dd, J = 2.7, 9.5 Hz), 8.62(2H, s), 12.86(1H, s). 107  embedded image 2 NMR2; 6.44(1H, t, J = 6.8 Hz), 7.20-7.33(3H, m), 7.37-7.53(3H, m), 7.64(1H, dd, J = 2.0, 7.0 Hz), 8.95(2H, s), 12.74(1H, s). 108 0  embedded image 2 NMR1; 7.06(1H, d, J = 9.9 Hz), 7.23(1H, ddd, J = 12.2, 8.5, 3.3 Hz), 7.43-7.55(2H, m), 8.05(1H, d, J = 10.0 Hz), 9.11(2H, s), 13.38(1H, s). (226) TABLE-US-00024 TABLE 2-12 EX STR Prop DATA 109  embedded image 2 NMR1; 7.06(1H, d, J = 9.9 Hz), 7.14-7.25(1H, m), 7.45-7.58(2H, m), 8.05(1H, d, J = 9.9 Hz), 9.09(2H, s), 13.37(1H, s). 110  embedded image 2 NMR1; 7.06(1H, d, J = 9.9 Hz), 7.27-7.39(2H, m), 7.43(1H, tdd, J = 9.3, 7.8, 4.5 Hz), 8.06(1H, d, J = 9.9 Hz), 9.12(2H, s), 13.38(1H, s). 111  embedded image 2 NMR1; 7.06(1H, d, J = 9.8 Hz), 7.26(1H, ddd, J = 8.2, 2.3, 1.0 Hz), 7.37 (1H, ddd, J = 8.1, 2.0, 1.0 Hz), 7.42-7.54(2H, m), 8.08(1H, d, J = 9.9 Hz), 9.09(2H, s), 13.36(1H, s). 112  embedded image 2 NMR1; 7.07(1H, d, J = 9.9 Hz), 7.62-7.73(2H, m), 7.72-7.62(1H, m), 7.86-7.92(1H, m), 8.06(1H, d, J = 9.9 Hz), 9.10(2H, s), 13.37(1H, s). 113  embedded image 2 NMR1; 7.06(1H, d, J = 9.9 Hz), 7.53(1H, ddd, J = 8.3, 4.7, 0.7 Hz), 7.78(1H, ddd, J = 8.3, 2.8, 1.4 Hz), 8.06(1H, d, J = 9.9 Hz), 8.51(1H, dd, J = 4.7, 1.4 Hz), 8.57(1H, d, J = 2.5 Hz), 9.10(2H, s), 13.37(1H, s). 114  embedded image 114 NMR1; 7.20-7.33(3H, m), 7.42-7.52(2H, m), 7.78(1H, d, J = 4.2 Hz), 8.01(1H, d, J = 4.2 Hz), 9.13(2H, s), 13.39(1H, s). 115  embedded image 114 NMR1; 7.09-7.20(2H, m), 7.25(1H, td, J = 2.3, 10.1 Hz), 7.45-7.56(1H, m), 7.79(1H, d, J = 4.2 Hz), 8.02(1H, d, J = 4.2 Hz), 9.15(2H, s), 13.40(1H, s). 116  embedded image 1 NMR2; 7.08(1H, d, J = 2.2 Hz), 7.18-7.27(2H, m), 7.27-7.37(1H, m), 7.43-7.53(2H, m), 8.02(1H, d, J = 2.2 Hz), 8.79(2H, s), 10.86(1H, s). 117  embedded image 114 NMR2; 7.17-7.35(4H, m), 7.40(1H, d, J = 4.1 Hz), 7.91(1H, d, J = 4.1 Hz), 9.07(2H, s), 10.59(1H, s). (227) TABLE-US-00025 TABLE 2-13 EX STR Prop DATA 118 0  embedded image 118 NMR3; 7.23-7.34(3H, m), 7.42-7.52(2H, m), 7.57(1H, d, J = 4.5 Hz), 7.68(1H, ddd, J = 1.3, 6.9 8.4 Hz), 7.86(1H, ddd, J = 1.4, 6.9, 8.4 Hz), 7.91- 7.98 (1H, m), 8.11-8.18(1H, m), 8.80(2, s), 8.94(1H, d, J = 4.5 Hz). 119  embedded image 119 NMR2; 7.20-7.35(4H, m), 7.42-7.52(2H, m), 7.66-7.79(3H, m), 8.30(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 120  embedded image 1 NMR2; 7.10-7.18(2H, m), 7.18-7.25(2H, m), 7.31(1H, dd, J = 9.3, 1.9 Hz), 7.66-7.80(3H, m), 8.30(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 121  embedded image 1 NMR2; 7.19-7.38(5H, m), 7.66-7.79(3H, m), 8.30(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 122  embedded image 1 NMR2; 6.96-7.09(3H, m), 7.31(1H, dd, J = 9.3, 1.8 Hz), 7.37-7.48(1H, m), 7.67-7.80(3H, m), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.76(2H, s). 123  embedded image 123 NMR2; 7.22-7.35(3H, m), 7.39(1H, d, J = 9.5 Hz), 7.43-7.53(2H, m), 7.85(1H, d, J = 1.2 Hz), 8.03- 8.12(2H, m), 9.13(2H, s). 124  embedded image 1 NMR2; 7.19-7.37(4H, m), 7.40(1H, d, J = 9.5 Hz), 7.85(1H, d, J = 1.2 Hz), 8.03-8.12(2H, m), 9.13(2H, s). 125  embedded image 1 NMR2; 6.97-7.10(3H, m), 7.37-7.49(2H, m), 7.86(1H, d, J = 1.2 Hz), 8.04-8.14(2H, m), 9.15(2H, s). 126  embedded image 1 NMR2; 7.12-7.19(2H, m), 7.19-7.25(2H, m), 7.39(1H, d, J = 9.4 Hz), 7.85(1H, d, J = 1.2 Hz), 8.03- 8.13(2H, m), 9.13(2H, s). 127  embedded image 1 NMR2; 6.98(1H, dd, J = 7.1, 1.8 Hz), 7.20-7.35(3H, m), 7.42-7.62(2H, m), 7.62-7.68(1H, m), 7.72(1H, d, J = 1.2 Hz), 7.77-7.83(1H, m), 8.25(1H, dd, J = 7.1, 1.0 Hz), 8.53

(2H, s).



(228) TABLE-US-00026 TABLE 2-14 EX STR Prop DATA 128 0  embedded image 1 NMR2; 7.21-7.28(2H, m), 7.32(1H, ddt, J = 7.9, 7.0, 1.1 Hz), 7.43-7.54(2H, m), 7.67(1H, d, J = 1.4 Hz), 7.92(1H, d, J = 1.4 Hz), 8.61(1H, d, J = 2.5 Hz), 8.71(1H, d, J = 2.5 Hz), 8.78(2H, s). 129  embedded image 1 NMR2; 7.21-7.28(2H, m), 7.32(1H, ddt, J = 7.6, 5.9, 1.2 Hz), 7.39-7.53(3H, m), 7.95(1H, dt, J = 9.5, 1.0 Hz), 8.30(1H, dd, J = 1.6, 1.1 Hz), 8.77(2H, s), 8.94(1H, d, J = 0.9 Hz). 130  embedded image 1 NMR2; 6.99(1H, dd, J = 7.1, 1.9 Hz), 7.18-7.37(4H, m), 7.62-7.68(1H, m), 7.72(1H, d, J = 1.2 Hz), 7.77-7.83(1H, m), 8.25(1H, dd, J = 7.1, 1.0 Hz), 8.63(2H, s). 131  embedded image 1 NMR2; 6.95-7.10(4H, m), 7.37-7.45(1H, m), 7.63-7.68(1H, m), 7.73(1H, d, J = 1.2 Hz), 7.81(1H, dt, J = 1.7, 0.8 Hz), 8.26 (1H, dd, J = 7.1, 1.0 Hz), 8.84(2H, s). 132  embedded image 1 NMR2; 6.98(1H, dd, J = 7.1, 1.8 Hz), 7.10-7.25(4H, m), 7.63-7.68(1H, m), 7.72(1H, d, J = 1.2 Hz), 7.80(1H, dt, J = 1.9, 0.9 Hz), 8.26(1H, dd, J = 7.1, 1.0 Hz), 8.83(2H, s). 133  embedded image 1 NMR2; 7.20-7.35(3H, m), 7.43-7.53(2H, m), 8.21(1H, s), 8.24(1H, d, J = 2.1 Hz), 8.75(1H, d, J = 2.2 Hz), 8.81(2H, s), 11.25(1H, s). 134  embedded image 1 NMR2; 6.75(1H, dd, J = 2.4, 0.9 Hz), 7.18(1H, d, J = 7.4 Hz), 7.23-7.36(3H, m), 7.43-7.53(2H, m), 8.18(1H, d, J = 2.4 Hz), 8.77(1H, dd, J = 7.3, 0.9 Hz), 9.25(2H, s). 135  embedded image 1 NMR2; 7.18-7.36(4H, m), 7.43-7.53(2H, m), 7.93(1H, dd, J = 1.9, 0.9 Hz), 8.42(1H, s), 8.72(1H, dd, J = 7.1, 0.9 Hz), 8.87(2H, s). 136  embedded image 1 NMR2; 6.77(1H, dd, J = 6.9, 1.1 Hz), 7.23-7.37(4H, m), 7.44-7.54(2H, m), 7.55-7.60(1H, m), 7.67- 7.75(2H, m), 8.84(2H, s). 137  embedded image 137 NMR2; 6.82(1H, ddd, J = 3.2, 2.0, 1.0 Hz), 7.21- 7.34(3H, m), 7.42-7.52(2H, m), 7.55(1H, dd, J = 3.4, 2.7 Hz), 7.80(1H, dd, J = 2.0, 1.0 Hz), 8.65(1H, d, J = 2.0 Hz), 8.78(1H, d, J = 8.7 Hz), 8.80(2H, s).











(229) TABLE-US-00027 TABLE 2-15 EX STR Prop DATA 138 0  embedded image 137 NMR2; 6.66(1H, dd, J = 3.5, 1.8 Hz), 7.17(1H, d, J = 5.0 Hz), 7.24-7.35(3H, m), 7.44-7.54(3H, m), 8.44(1H, d, J = 5.0 Hz), 8.96(2H, s), 10.69(1H, s). 139  embedded image 139 NMR1; 7.26-7.35(3H, m), 7.45-7.55(2H, m), 7.66(1H, dd, J = 4.2, 8.4 Hz), 7.73(1H, d, J = 4.4 Hz), 8.40(1H, dd, J = 1.9, 8.4 Hz), 8.90(2H, s), 9.18(1H, dd, J = 1.9, 4.1 Hz), 9.19(1H, d, J = 4.4 Hz). 140  embedded image 1 NMR2; 3.99(2H, s), 7.00(1H, s), 7.19(1H, dd, J = 9.2, 1.9 Hz), 7.21-7.34(3H, m), 7.41-7.51(3H, m), 8.09(1H, dd, J = 1.9, 0.9 Hz), 8.71(2H, s). 141  embedded image 1 NMR2; 7.23-7.26(2H, m), 7.31(1H, ddt, J = 7.9, 7.0, 1.1 Hz), 7.43-7.53(2H, m), 7.68(1H, dd, J = 9.2, 1.8 Hz), 7.92(1H, dd, J = 9.2, 1.0 Hz), 8.42(1H, s), 8.76-8.81(3H, m). 142  embedded image 1 NMR2; 4.03(3H, s), 7.20-7.34(4H, m), 7.40- 7.59(2H, m), 7.61-7.71(3H, m), 8.26-8.33(2H, m). 143  embedded image 139 NMR1; 7.35-7.36(3H, m), 7.44-7.55(2H, m), 7.84(1H, dd, J = 4.1, 8.5 Hz), 8.41-8.63(2H, m), 8.67(1H, d, J = 8.7 Hz), 9.02(1H, dd, J = 1.6, 4.1 Hz), 9.47(2H, s). 144  embedded image 1 NMR2; 7.19-7.38(4H, m), 7.89(1H, dd, J = 9.2, 1.8 Hz), 7.92(1H, dd, J = 9.2, 1.0 Hz), 8.42(1H, s), 8.77-8.83(3H, m). 145  embedded image 1 NMR2; 6.97-7.10(3H, m), 7.35-7.48(1H, m), 7.69(1H, dd, J = 9.2, 1.8 Hz), 7.93(1H, dd, J = 9.3, 1.0 Hz), 8.43(1H, s), 8.77-8.84(3H, m). 146  embedded image 1 NMR2; 7.10-7.25(4H, m), 7.68(1H, dd, J = 9.2, 1.5 Hz), 7.92(1H, dd, J = 9.3, 1.0 Hz), 8.43(1H, s), 8.77-8.81(3H, m). 147  embedded image 1 NMR2; 4.00(2H, s), 8.57(1H, dd, J = 6.9, 1.9 Hz), 6.95(1H, s), 7.20-7.34(3H, m), 7.41-7.53(3H, m), 8.00-8.06(1H, m), 8.80(2H, s). 148 0  embedded image 1 NMR2; 7.21-7.34(3H, m), 7.42-7.52(2H, m), 7.77-7.82(1H, m), 7.88(1H, d, J = 1.1 Hz), 8.45(1H, d, J = 1.5 Hz), 9.10(2H, s), 9.20(1H, dd, J = 1.6, 0.7 Hz).











(230) TABLE-US-00028 TABLE 2-16 EX STR Prop DATA 149  embedded image 1 NMR2; 7.18-7.38(4H, m), 7.77-7.83(1H, m), 7.88(1H, d, J = 1.1 Hz), 8.45(1H, d, J = 1.6 Hz), 9.10(2H, s), 9.20(1H, dd, J = 1.6, 0.7 Hz). 150  embedded image 1 NMR2; 6.96-7.10(3H, m), 7.37-7.48(1H, m), 7.81(1H, s), 7.89(1H, d, J = 1.1 Hz), 8.47 (1H, d, J = 1.5 Hz), 9.11(2H, s), 9.17-9.23(1H, m). 151  embedded image 1 NMR2; 6.60(1H, dd, J = 2.3, 0.9 Hz), 7.21-7.35(4H, m), 7.42-7.52(2H, m), 7.67(1H, dd, J = 9.2, 0.9 Hz), 8.02(1H, d, J = 2.3 Hz), 8.63-8.69(1H, m), 8.77(2H, s). 152  embedded image 1 NMR2; 6.60(1H, dd, J = 2.3, 0.9 Hz), 7.20-7.37(5H, m), 7.68(1H, dd, J = 9.2,



1.0 Hz), 8.02(1H, d, J = 2.3 Hz), 8.63-8.69(1H, m), 8.77(2H, s). 153  embedded image 1 NMR2; 6.51(1H, dd, J = 2.3, 0.9 Hz), 6.96-7.10(3H, m), 7.26(1H, dd, J = 9.1, 1.7 Hz), 7.37-7.48(1H, m), 7.68(1H, dd, J = 9.2, 1.0 Hz), 6.02(1H, d, J = 2.3 Hz), 8.64-8.70(1H, m), 8.79(2H, s). 154  embedded image 1 NMR2; 0.60(1H, dd, J = 2.3, 0.9 Hz), 7.10-7.18(2H, m), 7.18-7.29(3H, m), 7.68(1H, dd, J = 9.1, 1.0 Hz), 8.02(1H, d, J = 2.3 Hz), 8.63-8.89(1H, m), 8.77(2H, s). 155  embedded image 1 NMR2; 6.86(1H, dd, J = 9.4, 1.5 Hz), 7.21-7.27(2H, m), 7.27-7.34(1H, m), 7.42-7.53(3H, m), 7.54- 7.62(1H, m), 8.05-8.11(1H, m), 8.19-8.24(1H, m), 6.74(2H, s). 156  embedded image 1 NMR2; 6.66(1H, dd, J = 9.3, 1.5 Hz), 7.18-7.37(4H, m), 7.48-7.53(1H, m), 7.55-7.62(1H, m), 8.05- 8.11(1H, m), 8.19-8.24(1H, m), 8.74(2H, s). 157  embedded image 1 NMR2; 6.86(1H, dd, J = 9.4, 1.5 Hz), 6.98-7.09(3H, m), 7.42(1H, dtd, J = 8.8, 6.5, 1.6 Hz), 7.48-7.54(1H, m), 7.55-7.63(1H, m), 8.06-8.12(1H, m), 8.19-8.25(1H, m), 8.76(2H, s) 158 00  embedded image 1 NMR2; 6.85(1H, dd, J = 9.4, 1.5 Hz), 7.11-7.18(2H, m), 7.18-7.24(2H, m), 7.48-7.54(1H, m), 7.59(1H, dt, J = 9.4, 1.0 Hz), 8.05-8.11(1H, m), 8.19-8.24(1H, m), 8.74(2H, s). (231) TABLE-US-00029 TABLE 2-17 EX STR Prop DATA 159 01  embedded image 1 NMR2; 4.04(3H, s), 7.20-7.34(3H, m), 7.37- 7.51(3H, m), 7.80-7.88(1H, m), 8.29-8.33(1H, m), 6.33(1H, s), 8.85-8.90(1H, m). 160 02  embedded image 1 NMR2; 4.05(3H, s), 7.22-7.33(3H, m), 7.42-7.48(2H, m), 7.51(1H, d, J = 9.5 Hz), 7.80(1H, d, J = 1.2 Hz), 7.97(1H, dd, J = 9.5, 0.7 Hz), 8.01(1H, dd, J = 1.3, 0.7 Hz), 8.74(1H, s). 161 03  embedded image 1 NMR2; 2.41(3H, d, J = 0.8 Hz), 7.01-7.08(2H, m), 7.11(1H, dtd, J = 7.5, 1.6, 0.9 Hz), 7.28-7.39(2H, m), 7.67-7.70(1H, m), 7.72(1H, d, J = 1.2 Hz), 7.75(1H, dt, J = 9.4, 0.9 Hz), 8.29(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 162 04  embedded image 1 NMR2; 3.83(3H, s), 6.78-6.82(1H, m), 6.84(2H, dddd, J = 8.0, 4.2, 2.4, 0.9 Hz), 7.31(1H, dd, J = 9.3, 1.8 Hz), 7.37(1H, t, J = 8.2 Hz), 7.67-7.70(1H, m), 7.72(1H, d, J = 1.3 Hz), 7.76(1H, dt, J = 9.4, 0.9 Hz), 8.30(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 163 05  embedded image 163 NMR2; 7.16(1H, ddd, J = 8.1, 2.2, 1.1 Hz), 7.25- 7.35(3H, m), 7.36-7.43(1H, m), 7.68-7.71(1H, m), 7.73(1H, d, J = 1.2 Hz), 7.77(1H, dt, J = 9.3, 0.9 Hz), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.76(2H, s). 164 06  embedded image 163 NMR2; 7.06-7.23(3H, m), 7.31(1H, dd, J = 9.4, 1.9 Hz), 7.67-7.80(3H, m), 8.29-8.34(1H, m), 8.76(2H, s). 165 07  embedded image 163 NMR2; 6.91-7.05(2H, m), 7.23-7.35(2H, m), 7.68-7.71(1H, m), 7.72(1H, d, J = 1.3 Hz), 7.76(1H, dt, J = 9.4, 0.9 Hz), 8.30(1H, dd, J = 1.9, 1.0 Hz), 8.74(2H, s). 166 08  embedded image 163 NMR2; 6.99(1H, dtd, J = 9.1, 7.7, 8.3 Hz), 7.08(1H, ddd, J = 8.3, 6.1, 3.1 Hz), 7.19(1H, td, J = 9.4, 5.0 Hz), 7.31(1, dd, J = 9.3, 1.9 Hz), 7.68- 7.71(1H, m), 7.72(1H, d, J = 1.2 Hz), 7.76(1H, dt, J = 9.3, 0.9 Hz), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). 167 09  embedded image 163 NMR2; 7.00-7.12(2H, m), 7.19-7.23(1H, m), 7.31(1H, dd, J = 9.3, 1.8 Hz), 7.68-7.71(1H, m), 7.72(1H, d, J = 1.3 Hz), 7.74-7.79(1H, m), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.75(2H, s). (232) TABLE-US-00030 TABLE 2-18 EX STR Prop DATA 168 0  embedded image 163 NMR2; 7.00(1H, dddd, J = 9.0, 3.6, 2.8, 1.8 Hz), 7.13(1H, ddd, J = 10.7, 6.7, 2.8 Hz), 7.25(1H, dt, J = 9.6, 8.9 Hz), 7.31(1H, dd, J = 9.4, 1.6 Hz), 7.68- 7.72(1H, m), 7.73(1H, d, J = 1.3 Hz), 7.74-7.80(1H, m), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.76(2H,s). 169  embedded image 163 NMR2; 6.76(1H, tt, J = 8.9, 2.3 Hz), 6.80-6.87(2H, m), 7.32(1H, dd, J = 9.3, 1.9 Hz), 7.69-7.72(1H, m), 7.73(1H, d, J = 1.3 Hz), 7.76-7.79(1H, m), 8.32(1H, dd, J = 1.8, 1.0 Hz), 8.78(2H, s). 170  embedded image 163 NMR2; 7.32(1H, dd, J = 9.3, 1.9 Hz), 7.41-7.48(1H, m), 7.50-7.64(3H, m), 7.68-7.71(1H, m), 7.73(1H, d, J = 1.3 Hz), 7.74-7.81(1H, m), 8.32(1H, dd, J = 1.8, 1.0 Hz), 8.77(2H, s). 171  embedded image 163 NMR2; 7.14-7.19(2H, m), 7.21(1H, ddd, J = 8.3, 2.1, 1.1 Hz), 7.32(1H, dd, J = 9.4, 1.9 Hz), 7.44- 7.53(1H, m), 7.68-7.71(1H, m), 7.73(1H, d, J = 1.3 Hz), 7.74-7.79(1H, m), 8.31(1H, dd, J = 1.9, 1.0 Hz), 8.77(2H, s). 172  embedded image 172 NMR2; 3.74(2H, s), 7.19-7.33(4H, m), 7.41- 7.54(3H, m), 6.12(1H, s), 9.07(2H, s). 173  embedded image 173 NMR2; 7.21-7.28(2H, m), 7.28-7.36(1H, m), 7.41(1H, dd, J = 9.1, 1.5 Hz), 7.45-7.51(2H, m), 7.88(1H, dd, J = 9.2, 1.0 Hz), 8.14(1H, d, J = 1.0 Hz), 8.82(2H, s), 8.88-8.94(1H, m). 174  embedded image 1 NMR2; 7.20-7.38(4H, m), 7.41(1H, dd, J = 9.2, 1.5 Hz), 7.88(1H, dd, J = 9.2, 1.1 Hz), 6.14(1H, d, J = 1.1 Hz), 8.82(2H, s), 8.92(1H, q, J = 1.1 Hz). 175  embedded image 1 NMR2; 6.97-7.10(3H,





















m), 7.38-7.49(2H, m), 7.89(1H, dd, J = 9.2, 1.1 Hz), 8.15(1H, d, J = 1.0 Hz), 8.83(2H, s), 8.93(1H, q, J = 1.1 Hz). 176  embedded image 1 NMR2; 7.10-7.27(4H, m), 7.41(1H, dd, J = 9.1, 1.5 Hz), 7.88(1H, dd, J = 9.2, 1.0 Hz), 8.15(1H, d, J = 1.0 Hz), 8.82(2H, s), 8.92(1H, q, J = 1.1 Hz). 177  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 7.20-7.34(4H, m), 7.41-7.52(3H, m), 7.63(1H, dt, J = 9.3, 0.9 Hz), 8.19(1H, dd, J = 1.9, 1.0 Hz), 8.73(2H, s).









(233) TABLE-US-00031 TABLE 2-19 EX STR Prop DATA 178 0  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 7.18-7.37(5H, m), 7.41-7.48(1H, m), 7.59-7.67(1H, m), 8.20(1H, dd, J = 1.9, 1.0 Hz), 8.73(2H, s). 179  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 6.96-7.09(3H, m), 7.26(1H, dd, J = 9.3, 1.8 Hz), 7.36-7.47(2H, m), 7.60-7.68(1H, m), 6.20(1H, dd, J = 1.9, 1.0 Hz), 8.74(2H, s). 180  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 7.09-7.28(6H, m), 7.41-7.46(1H, m), 7.59-7.67(1H, m), 8.19(1H, dd, J = 1.8, 1.0 Hz), 8.73(2H, s). 181  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 6.92(1H, dd, J = 7.0, 1.9 Hz), 7.20-7.33(3H, m), 7.37-7.42(1H, m), 7.43-7.51(2H, m), 7.64-7.70(1H, m), 8.14(1H, dd, J = 7.0, 0.9 Hz), 8.81(2H, s). 182  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 6.92(1H, dd, J = 7.0, 1.8 Hz), 7.18-7.37(4H, m), 7.37-7.42(1H, m), 7.64-7.70(1H, m), 8.14(1H, dd, J = 7.0, 0.9 Hz), 8.81(2H, s). 183  embedded image 1 NMR2; 2.49(3H, d, J = 0.9 Hz), 6.92(1H, dd, J = 7.0, 1.9 Hz), 6.95-7.09(3H, m), 7.36-7.47(2H, m), 7.65-7.70(1H, m), 8.15(1H, dd, J = 7.0, 1.0 Hz), 8.62(2H, s). 184  embedded image 1 NMR2; 7.15(1H, dd, J = 7.3, 1.9 Hz), 7.20-7.29(2H, m), 7.31(1H, ddt, J = 7.8, 6.9, 1.1 Hz), 7.43-7.53(2H, m), 7.87(1H, dd, J = 1.9, 1.0 Hz), 8.17(1H, d, J = 1.0 Hz), 8.82-8.90(3H, m). 185  embedded image 1 NMR2; 7.16(1H, dd, J = 7.3, 1.9 Hz), 7.19-7.37(4H, m), 7.88(1H, dd, J = 1.9, 1.0 Hz), 8.17(1H, d, J = 1.0 Hz), 6.84(2H, s), 8.86(1H, dt, J = 7.3, 1.0 Hz). 186  embedded image 1 NMR2; 6.97-7.10(3H, m), 7.16(1H, dd, J = 7.3, 1.9 Hz), 7.43(1H, tdd, J = 8.2, 6.5, 0.6 Hz), 7.89(1H, dd, J = 1.9, 1.0 Hz), 8.18(1H, d, J = 1.0 Hz), 8.53-8.91(3H, m). 187  embedded image 1 NMR2; 7.10-7.26(5H, m), 7.88(1H, dd, J = 1.9, 1.0 Hz), 8.17(1H, d, J = 1.0 Hz), 8.81-8.90(3H, m).

(234) TABLE-US-00032 TABLE 2-20 EX STR Prop DATA 188 0  embedded image 1 NMR2; 7.21-7.28(2H, m), 7.33(1H, ddt, J = 7.9, 7.0, 1.1 Hz), 7.44-7.54(2H, m), 8.61(1H, s), 8.82(2H, s), 8.98-9.05(2H, m). 189  embedded image 1 NMR2; 6.97-7.10(3H, m), 7.44(1H, td, J = 8.2, 6.5 Hz), 8.61(1H, s), 8.83(2H, s), 9.00-9.05(2H, m). 190  embedded image 1 NMR2; 2.54(3H, d, J = 1.0 Hz), 7.21-7.35(4H, m), 7.42-7.52(3H, m), 7.73(1H, dd, J = 9.3, 1.0 Hz), 7.99(1H, dd, J = 1.9, 1.0 Hz), 8.77(2H, s). 191  embedded image 1 NMR2; 2.54(3H, d, J = 0.9 Hz), 7.19-7.37(6H, m), 7.47-7.52(1H, m), 7.73(1H, dd, J = 9.3, 1.0 Hz), 7.99(1H, dd, J = 1.8, 1.0 Hz), 8.77(2H, s). 192  embedded image 1 NMR2; 2.54(3H, s), 6.96-7.09(3H, m), 7.29(1H, dd, J = 9.3, 1.7 Hz), 7.42(1H, dddd, J = 9.4, 6.0, 6.2, 1.6 Hz), 7.50(1H, s), 7.74(1H, d, J = 9.4 Hz), 7.97-8.03(1H, m), 8.76-8.81(2H, m). 193  embedded image 1 NMR2; 2.54(3H, d, J = 1.0 Hz), 7.10-7.18(2H, m), 7.18-7.25(2H, m), 7.29(1H, dd, J = 9.3, 1.8 Hz), 7.50(1H, s), 7.73(1H, dd, J = 9.3, 1.0 Hz), 7.99(1H, dd, J = 1.8, 1.0 Hz), 8.77(2H, s). 194  embedded image 1 NMR2; 6.63(1H, dd, J = 2.3, 0.9 Hz), 6.91(1H, dd, J = 7.3, 2.0 Hz), 7.22-7.27(2H, m), 7.28-7.35(1H, m), 7.42-7.52(2H, m), 7.69(1H, dd, J = 2.0, 1.0 Hz), 8.02(1H, d, J = 2.3 Hz), 8.58(1H, dt, J = 7.3, 1.0 Hz), 8.82(2H, s). 195  embedded image 1 NMR2; 6.63(1H, dd, J = 2.3, 0.9 Hz), 6.91(1H, dd, J = 7.3, 2.0 Hz), 7.18-7.37(4H, m), 7.70(1H, dd, J = 2.1, 0.9 Hz), 8.02(1H, d, J = 2.3 Hz), 8.58(1H, dt, J = 7.3, 0.9 Hz), 8.81(2H, s). 196  embedded image 1 NMR2; 6.64(1H, dd, J = 2.3, 0.9 Hz), 6.92(1H, dd, J = 7.3, 2.1 Hz), 6.95-7.10(3H, m), 7.37-7.46(1H, m), 7.70(1H, dd, J = 2.1, 1.0 Hz), 8.02(1H, d, J = 2.3 Hz), 8.59(1H, dt, J = 7.3, 0.9 Hz), 8.83(2H, s). 197  embedded image 1 NMR2; 6.63(1H, dd, J = 2.3, 0.9 Hz), 6.91(1H, dd, J = 7.3, 2.0 Hz), 7.10-7.18(2H, m), 7.18-7.25(2H, m), 7.69(1H, dd, J = 2.1, 1.0 Hz), 8.02(1H, d, J = 2.3 Hz), 8.58(1H, dt, J = 7.3, 0.9 Hz), 8.82(2H, s).


(235) TABLE-US-00033 TABLE 2-21 EX STR Prop DATA 198 0  embedded image 198 NMR1; 2.75(3H, s), 7.24-7.35(3H, m), 7.44-7.54(2H, m), 7.97-8.06(2H, m), 8.41(1H, d, J = 2.2 Hz), 8.52(1H, dd, J = 2.3, 0.7 Hz), 8.85(2H, s), 15.13(1H, s). 199  embedded image 198 NMR1; 2.73(3H, s), 7.27-7.52(4H, m), 5.01(2H, s), 8.35-8.41(1H, m), 8.51(1H, d, J = 2.2 Hz), 5.84(2H, s),











14.98(1H, s). 200  embedded image 198 NMR1; 2.75(3H, s), 7.12-7.22(2H, m), 7.28(1H, dt, J = 10.1, 2.3 Hz), 7.53(1H, td, J = 8.3, 6.8 Hz), 7.93-8.08(2H, m), 8.41(1H, d, J = 2.2 Hz), 8.50-8.56(1H, m), 8.83(2H, s), 15.14(1H, s). 201  embedded image 1 NMR2; 2.58(3H, s), 7.08-7.19(3H, m), 7.20-7.28(2H, m), 7.55-7.61(1H, m), 7.63-7.70(1H, m), 7.78(1H, d, J = 1.3 Hz), 8.58(2H, s). 202  embedded image 198 NMR1; 2.49(3H, s), 2.57(3H, d, J = 0.9 Hz), 7.28-7.51(4H, m), 8.04(1H, dd, J = 9.3, 0.9 Hz), 8.27(1H, dd, J = 9.3, 1.7 Hz), 9.08-9.12(1H, m), 9.18(2H, s), 14.92(1H, s). 203  embedded image 1 NMR2; 2.458(3H, s), 2.463(3H, s), 7.09-7.27(5H, m), 7.63(1H, dd, J = 9.2, 1.0 Hz), 7.90(1H, dd, J = 1.8, 1.0 Hz), 8.76(2H, s). 204  embedded image 1 NMR2; 2.45(3H, s), 2.46(3H, s), 6.98(1H, dd, J = 7.1, 1.9 Hz), 7.20-7.34(3H, m), 7.41-7.52(2H, m), 7.67(1H, dd, J = 1.9, 0.9 Hz), 7.90(1H, dd, J = 7.1, 0.9 Hz), 8.82(2H, s). 205  embedded image 1 NMR2; 2.45(3H, s), 2.46(3H, s), 6.98(1H, dd, J = 7.1, 1.9 Hz), 7.19-7.37(4H, m), 7.67(1H, dd, J = 1.9, 0.9 Hz), 7.90(1H, dd, J = 7.1, 0.9 Hz), 8.82(2H, s). 206  embedded image 1 NMR2; 2.45(3H, s), 2.46(3H, s), 6.95-7.09(4H, m), 7.36-7.47(1H, m), 7.88(1H, dd, J = 1.9, 0.9 Hz), 7.91(1H, dd, J = 7.1, 1.0 Hz), 8.83(2H, s). 207  embedded image 1 NMR2; 2.45(3H, s), 2.46(3H, s), 6.95(1H, dd, J = 7.1, 1.9 Hz), 7.10-7.18(2H, m), 7.18-7.26(2H, m), 7.67(1H, dd, J = 1.9, 0.9 Hz), 7.91(1H, dd, J = 7.2, 1.0 Hz), 5.81(2H, s).











(236) TABLE-US-00034 TABLE 2-22 EX STR Prop DATA 208 0  embedded image 1 NMR2; 3.51(3H, s), 4.68(2H, d, J = 0.8 Hz), 7.20-7.34(4H, m), 7.42-7.52(2H, m), 7.63-7.73(2H, m), 8.24(1H, dd, J = 1.8, 1.0 Hz), 8.74(2H, s). 209  embedded image 1 NMR2; 3.51(3H, s), 4.68(2H, s), 7.18-7.37(5H, m), 7.64-7.73(2H, m), 8.25(1H, dd, J = 1.9, 1.0 Hz), 8.74(2H, s). 210  embedded image 1 NMR2; 3.51(3H, s), 4.68(2H, d, J = 0.8 Hz), 6.96-7.09(3H, m), 7.30(1H, dd, J = 9.3, 1.8 Hz), 7.38-7.48(1H, m), 7.64-7.74(2H, m), 8.26(1H, dd, J = 1.9, 1.0 Hz), 8.76(2H, s). 211  embedded image 1 NMR2; 7.07(1H, dd, J = 7.2, 1.7 Hz), 7.20-7.28(2H, m), 7.31(1H, ddt, J = 7.9, 7.0, 7.1, 1.1 Hz), 7.43-7.53(2H, m), 7.95(1H, dt, J = 1.8, 1.0 Hz), 8.25(1H, dd, J = 7.2, 1.1 Hz), 6.85(2H, s), 8.89(1H, d, J = 0.9 Hz). 212  embedded image 1 NMR2; 6.96-7.11(4H, m), 7.43(1H, tdd, J = 8.2, 6.5, 0.6 Hz), 7.97(1H, dt, J = 1.9, 1.0 Hz), 8.28(1H, dd, J = 7.2, 1.1 Hz), 8.87(2H, s), 8.89(1H, d, J = 0.9 Hz). 213  embedded image 1 NMR2; 7.07(1H, dd, J = 7.2, 1.7 Hz), 7.10-7.25(4H, m), 7.96(1H, dt, J = 1.9, 1.0 Hz), 8.27(1H, dd, J = 7.2, 1.1 Hz), 8.85(2H, s), 8.89(1H, d, J = 0.9 Hz). 214  embedded image 1 NMR2; 7.21-7.28(2H, m), 7.28-7.35(1H, m), 7.41-7.54(3H, m), 7.78-7.86(1H, m), 7.96-8.02(1H, m), 8.30(1H, dd, J = 1.8, 1.0 Hz), 8.75(2H, s). 215  embedded image 1 NMR2; 3.93(3H, s), 6.48(1H, d, J = 3.4 Hz), 7.21-7.33(4H, m), 7.41-7.51(3H, m), 7.98(1H, d, J = 8.1 Hz), 9.25(2H, s). 216  embedded image 1 NMR2; 7.12(1H, dd, J = 7.1, 1.8 Hz), 7.21-7.27(2H, m), 7.31(1H, ddt, J = 7.9, 7.0, 1.2 Hz), 7.43-7.53(2H, m), 7.81-7.87(1H, m), 7.92-7.98(1H, m), 8.28(1H, dd, J = 7.1, 1.0 Hz), 8.83(2H, s). 217  embedded image 1 NMR2; 7.12(1H, dd, J = 7.2, 1.9 Hz), 7.19-7.37(4H, m), 7.82-7.87(1H, m), 7.92-7.96(1H, m), 8.28(1H, dd, J = 7.2, 1.0 Hz), 8.83(2H, s).





(237) TABLE-US-00035 TABLE 2-23 EX STR Prop DATA 218 0  embedded image 1 NMR2; 6.96-7.09 (3H, m), 7.12 (1H, dd, J = 7.1, 1.8 Hz), 7.43 (1H, tdd, J = 8.2, 6.5, 0.7 Hz), 7.82-7.88 (1H, m), 7.93-7.99 (1H, m), 8.29 (1H, dd, J = 7.1, 1.0 Hz), 8.84 (2H, s). 219  embedded image 1 NMR2; 7.08-7.26 (5H, m), 7.81-7.87 (1H, m), 7.92-7.98 (1H, m), 8.28 (1H, dd, J = 7.1, 1.0 Hz), 8.83 (2H, s). 220  embedded image 220 NMR2; 2.09-2.20 (2H, m), 3.43-3.51 (2H, m), 3.66-3.74 (2H, m), 5.03 (1H, s), 7.15-7.30 (3H, m), 7.38-7.48 (2H, m), 8.55 (2H, s). 221  embedded image 221 NMR2; 2.10-2.21 (2H, m), 3.43-3.51 (2H, m), 3.68-3.75 (2H, m), 5.15 (1H, s), 6.91-7.04 (3H, m), 7.32-7.43 (1H, m), 8.57 (2H, s). 222  embedded image 220 NMR2; 1.92-2.07 (4H, m), 2.55-2.64 (2H, m), 3.63-3.72 (2H, m), 6.92-7.05 (3H, m), 7.33-7.44 (1H, m), 8.53 (2H, s). 223  embedded image 223 NMR2; 1.55-1.63 (2H, m), 1.69-1.78 (4H, m), 3.05-3.13 (4H, m), 7.13-7.25 (3H, m), 7.35-7.45 (2H, m), 8.21 (2H, s). 224  embedded image 223 NMR2; 3.07-3.15 (4H, m), 3.84-3.91 (4H, m), 7.14-7.27 (3H, m), 7.36-7.46 (2H, m), 8.21 (2H, s). 225  embedded image 223 NMR2; 3.08-3.15 (4H, m), 3.84-3.91 (4H, m), 7.03-7.19 (4H, m), 8.20 (2H, s). 226  embedded image 226 NMR2; 1.54-1.64 (1H, m), 1.73 (2H, dtd, J = 12.8, 8.9, 3.9 Hz), 1.97-2.09


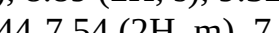
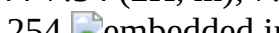

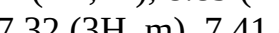
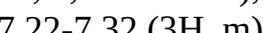


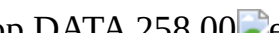
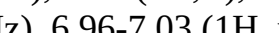
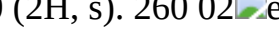
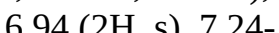

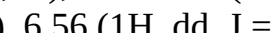
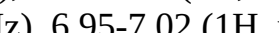
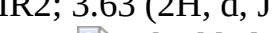
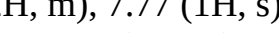
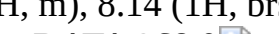
(2H, m), 2.94 (2H, ddd, J = 12.4, 9.3, 3.3 Hz), 3.38-3.49 (2H, m), 3.83- 3.95 (1H, m), 7.13-7.26 (3H, m), 7.36-7.46 (2H, m), 8.23 (2H, s). 227  embedded image 226 NMR2; 1.53 (1H, d, J = 4.2 Hz), 1.73 (2H, dtd, J = 12.8, 8.8, 3.9 Hz), 1.98-2.09 (2H, m), 2.96 (2H, ddd, J = 12.4, 9.2, 3.3 Hz), 3.40-3.51 (2H, m), 3.85- 3.97 (1H, m), 6.87-7.01 (3H, m), 7.29-7.41 (1H, m), 8.24 (2H, s).

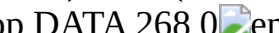
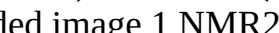
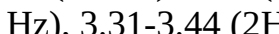
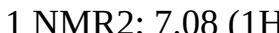
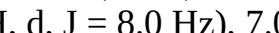
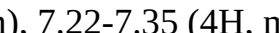
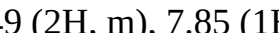

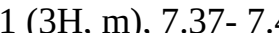

(238) TABLE-US-00036 TABLE 2-24 EX STR Prop DATA 228 0  embedded image 226 NMR2; 1.54 (1H, d, J = 4.2 Hz), 1.66-1.80 (2H, m), 1.97-2.09 (2H, m), 2.94 (2H, ddd, J = 12.4, 9.2, 3.3 Hz), 3.38-3.49 (2H, m), 3.84-3.96 (1H, m), 7.03-7.19 (4H, m), 8.22 (2H, s). 229  embedded image 229 NMR2; 3.75-3.83 (2H, m), 4.03-4.11 (2H, m), 4.37 (2H, s), 7.16-7.24 (2H, m), 7.24-7.32 (1H, m), 7.39-7.50 (2H, m), 8.61 (2H, s). 230  embedded image 229 NMR2; 3.76-3.84 (2H, m), 4.04-4.12 (2H, m), 4.37 (2H, s), 6.92-7.05 (3H, m), 7.34-7.45 (1H, m), 8.63 (2H, s). 231  embedded image 229 NMR2; 3.75-3.83 (2H, m), 4.04-4.11 (2H, m), 4.37 (2H, s), 7.06-7.22 (4H, m), 8.61 (2H, s). 232  embedded image 229 NMR2; 2.92-3.00 (2H, m), 3.83-3.89 (2H, m), 3.89-3.97 (4H, m), 7.17-7.23 (2H, m), 7.23- 7.30 (1H, m), 7.39-7.48 (2H, m), 8.43 (2H, s). 233  embedded image 229 NMR2; 2.93-3.00 (2H, m), 3.84-3.97 (6H, m), 6.92-7.05 (3H, m), 7.34-7.44 (1H, m), 8.45 (2H, s). 234  embedded image 229 NMR2; 2.92-3.00 (2H, m), 3.83-3.90 (2H, m), 3.90-3.97 (4H, m), 7.06-7.21 (4H, m), 8.43 (2H, s). 235  embedded image 226 NMR2; 1.76-1.82 (1H, m), 2.02-2.24 (2H, m), 2.63 (1H, ddd, J = 17.7, 5.3, 1.6 Hz), 2.86 (1H, ddd, J = 17.7, 4.6, 1.1 Hz), 3.58 (1H, dt, J = 11.5, 5.5 Hz), 3.94 (1H, ddd, J = 11.7, 8.7, 4.8 Hz), 4.36- 4.45 (1H, m), 7.16-7.31 (3H, m), 7.39-7.49 (2H, m), 8.52 (2H, s). 236  embedded image 7 NMR2; 6.03 (2H, s), 6.89-6.94 (1H, m), 6.95- 6.99 (2H, m), 7.19-7.32 (3H, m), 7.40-7.50 (2H, m), 8.67 (2H, s). 237  embedded image 7 NMR2; 7.21-7.35 (3H, m), 7.43-7.51 (2H, m), 7.60-7.66 (1H, m), 7.70-7.78 (2H, m), 7.78- 7.82 (1H, m), 8.75 (2H, s).

(239) TABLE-US-00037 TABLE 2-25 EX STR Prop DATA 238 0  embedded image 1 NMR2; 2.87 (3H, s), 7.21-7.33 (3H, m), 7.42- 7.54 (3H, m), 7.91-7.96 (1H, m), 8.06-8.12 (1H, m), 8.82 (2H, s). 239  embedded image 239 NMR2; 3.86 (2H, s), 6.77-6.85 (2H, m), 7.22- 7.39 (5H, m), 7.43-7.52 (2H, m), 8.71 (2H, s). 240  embedded image 240 NMR2; 3.98 (2H, s), 6.84 (1H, dd, J = 8.6, 0.8 Hz), 7.00 (1H, dd, J = 8.5, 0.7 Hz), 7.05-7.19 (4H, m), 7.72 (1H, dd, J = 8.6, 2.6 Hz), 7.83 (1H, dd, J = 8.5, 2.6 Hz), 8.30-8.35 (2H, m). 241  embedded image 1 NMR2; 7.22-7.34 (3H, m), 7.42-7.53 (2H, m), 7.57-7.65 (1H, m), 8.09 (1H, dd, J = 8.3, 0.6 Hz), 8.30 (1H, dd, J = 1.8, 0.6 Hz), 8.85 (2H, s), 9.08 (1H, s). 242  embedded image 1 NMR2; 7.19-7.34 (3H, m), 7.42-7.52 (2H, m), 7.67 (1H, dd, J = 8.5, 1.9 Hz), 8.10 (1H, dd, J = 1.8, 0.6 Hz), 8.25 (1H, dd, J = 8.5, 0.6 Hz), 8.82 (2H, s), 9.06 (1H, s). 243  embedded image 7 NMR1; 7.21-7.33 (3H, m), 7.42-7.52 (3H, m), 7.81-7.88 (2H, m), 7.95-8.03 (2H, m), 8.06 (1H, s), 9.04 (2H, s). 244  embedded image 1 NMR2; 7.24-7.35 (3H, m), 7.43-7.53 (3H, m), 7.73 (1H, dd, J = 1.9, 8.4 Hz), 7.96 (1H, d, J = 8.4 Hz), 8.18-8.26 (1H, m), 8.26-8.31 (1H, m), 8.93 (2H, s), 8.98 (1H, dd, J = 1.8, 4.3 Hz). 245  embedded image 7 NMR2; 2.65-2.74 (2H, m), 3.01-3.10 (2H, m), 6.86 (1H, d, J = 8.7 Hz), 7.22-7.35 (5H, m), 7.41-7.51 (2H, m), 7.62 (1H, s), 8.71 (2H, s). 246  embedded image 7 NMR2; 2.64-2.73 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 6.86 (1H, s), 7.13 (1H, dd, J = 1.8, 7.7 Hz), 7.19- 7.34 (3H, m), 7.41-7.51 (2H, m), 7.83-7.96 (1H, m), 8.71 (2H, s). 247  embedded image 7 NMR2; 3.09 (2H, t, J = 6.6 Hz), 3.63 (2H, td, J = 2.9, 6.5 Hz), 5.93 (1H, s), 7.19-7.34 (3H, m), 7.34- 7.40 (1H, m), 7.42-7.55 (3H, m). 8.19 (1H, d, J = 8.0 Hz), 8.78 (2H, s).

(240) TABLE-US-00038 TABLE 2-26 EX STR Prop DATA 248 0  embedded image 1 NMR2; 7.26-7.36 (3H, m), 7.44-7.54 (2H, m), 7.61 (1H, dt, J = 1.0, 6.0 Hz), 7.66 (1H, dd, J = 1.3, 7.1 Hz), 7.72 (1H, dd, J = 7.1, 8.1 Hz), 8.09 (1H, dt, J = 1.2, 8.1 Hz), 8.57 (1H, d, J = 6.0 Hz), 8.70 (2H, s), 9.36 (1H, d, J = 1.0 Hz). 249  embedded image 1 NMR2; 7.27-7.36 (3H, m), 7.44-7.55 (3H, m), 7.72- 7.83 (2H, m), 7.93 (1H, dt, J = 1.1, 8.4 Hz), 8.63 (1H, d, J = 5.7 Hz), 8.73 (2H, s), 9.21-9.27 (1H, m). 250  embedded image 1 NMR2; 7.23-7.35 (3H, m), 7.43-7.53 (3H, m), 7.88 (1H, dd, J = 2.1, 8.7 Hz), 7.96 (1H, d, J = 2.2 Hz), 8.21-8.31 (2H, m), 8.89 (2H, s), 8.97 (1H, dd, J = 1.7, 4.2 Hz). 251  embedded image 1 NMR2; 7.22-7.35 (3H, m), 7.43-7.56 (2H, m), 7.73 (1H, dt, J = 1.0, 5.9 Hz), 7.77 (1H, dd, J = 1.8, 8.5 Hz), 7.94-7.99 (1H, m), 8.12 (1H, dt, J = 0.8, 8.5 Hz), 8.61 (1H,

d, J = 5.8 Hz), 8.89 (2H, s), 9.29- 9.35 (1H, m). 252  7.22-7.35 (3H, m), 7.43-7.55 (2H, m), 7.71 (1H, dt, J = 1.0, 5.8 Hz), 7.86 (1H, dd, J = 1.9, 8.5 Hz), 7.97 (1H, d, J = 8.4 Hz), 8.09-8.14 (1H, m), 8.59 (1H, d, J = 5.7 Hz), 8.89 (2H, s), 9.32-9.38 (1H, m). 253  7.23-7.36 (3H, m), 7.44-7.54 (2H, m), 7.96 (1H, dd, J = 2.1, 8.7 Hz), 8.22-8.31 (2H, m), 8.89-8.92 (2H, m), 8.94 (2H, s). 254  7.22-7.35 (3H, m), 7.43-7.53 (2H, m), 7.91 (1H, d, J = 8.5 Hz), 7.97 (1H, dd, J = 2.2, 8.5 Hz), 8.14 (1H, s), 8.45-8.51 (1H, m), 8.88 (2H, s), 11.11 (1H, s). 255  7.24-7.35 (3H, m), 7.44-7.53 (2H, m), 8.06- 8.13 (2H, m), 8.18-8.24 (1H, m), 8.89 (2H, s), 9.39 (1H, s), 9.49-9.53 (1H, m). 256  7.22-7.32 (3H, m), 7.41 (1H, d, J = 8.5 Hz), 7.44-7.50 (2H, m), 7.95 (1H, dd, J = 2.1, 8.5 Hz), 8.20 (1H, d, J = 2.1 Hz), 8.23 (1H, s), 9.05 (2H, s), 12.54 (1H, s). 257  7.22-7.32 (3H, m), 7.42-7.52 (2H, m), 7.58 (1H, dd, J = 8.4, 1.7 Hz), 7.73 (1H, d, J = 8.3 Hz), 7.97 (1H, d, J = 1.9 Hz), 8.39 (1H, s), 9.00 (2H, s) (NH and oxalic acid protons were not found).

(241) TABLE-US-00039 TABLE 2-27 EX STR Prop DATA 258 00  7.22-7.34 (3H, m), 7.43-7.51 (2H, m), 7.55 (1H, dd, J = 8.7, 1.7 Hz), 7.64 (1H, dt, J = 8.7, 1.0 Hz), 7.90 (1H, dd, J = 1.6, 0.9 Hz), 8.17 (1H, d, J = 1.1 Hz), 8.80 (2H, s), 10.24 (1H, s). 259 01  3.63 (2H, d, J = 1.0 Hz), 6.96-7.03 (1H, m). 7.20-7.33 (3H, m), 7.33-7.42 (2H, m), 7.42- 7.50 (2H, m), 8.31 (1H, s), 8.70 (2H, s). 260 02  3.84 (3H, s), 6.56 (1H, dd, J = 3.1, 0.9 Hz), 7.13 (1H, d, J = 3.1 Hz), 7.21-7.31 (3H, m), 7.35 (1H, dd, J = 8.5, 1.8 Hz), 7.39-7.51 (3H, m), 7.76 (1H, dd, J = 1.8, 0.7 Hz), 8.79 (2H, s). 261 03  6.68-6.75 (1H, m), 6.94 (2H, s), 7.24- 7.37 (3H, m), 7.43-7.53 (2H, m), 7.57 (1H, dd, J = 7.2, 8.3 Hz), 7.64 (1H, dd, J = 1.2, 7.2 Hz), 7.82 (1H, d, J = 6.0 Hz), 8.30 (1H, dt, J = 1.2, 8.3 Hz), 8.74 (2H, s). 262 04  6.64 (1H, ddd, J = 3.1, 2.0, 1.0 Hz), 7.22- 7.37 (5H, m), 7.41-7.55 (3H, m), 7.75-7.81 (1H, m), 8.30 (1H, s), 8.80 (2H, s). 263 05  3.85 (3H, s), 6.56 (1H, dd, J = 3.2, 0.9 Hz), 7.10-7.19 (2H, m), 7.24-7.37 (4H, m), 7.40 (1H, dt, J = 8.3, 1.0 Hz), 7.43-7.52 (2H, m), 8.87 (2H, s). 264 06  3.62 (2H, d, J = 1.0 Hz), 6.95-7.02 (1H, m), 7.17-7.44 (6H, m), 7.92 (1H, s), 8.70 (2H, s). 265 07  3.63 (2H, d, J = 1.0 Hz), 6.94-7.09 (4H, m), 7.34-7.47 (3H, m), 7.87 (1H, s), 8.71 (2H, s). 266 08  3.62 (2H, s), 6.95-7.02 (1H, m), 7.08- 7.25 (4H, m), 7.33-7.41 (2H, m), 7.77 (1H, s), 8.70 (2H, s). 267 09  3.58-3.63 (2H, m), 6.98-7.03 (1H, m), 7.16 (1H, dd, J = 7.7, 1.7 Hz), 7.20-7.32 (3H, m), 7.32-7.38 (1H, m), 7.41-7.51 (2H, m), 8.14 (1H, brs), 8.72 (2H, s).

(242) TABLE-US-00040 TABLE 2-28 EX STR Prop DATA 268 0  7.25-7.36 (3H, m), 7.45-7.54 (2H, m), 7.75- 7.81 (1H, m), 7.79-7.92 (2H, m), 8.30 (1H, d, J = 8.0 Hz), 8.82 (2H, s), 9.31-9.36 (1H, m). 269  3.58-3.68 (2H, m), 6.99-7.04 (1H, m), 7.16 (1H, dd, J = 7.7, 1.7 Hz), 7.18-7.38 (5H, m), 8.30 (1H, s), 8.72 (2H, s). 270  2.94 (2H, t, J = 7.5 Hz), 3.31-3.44 (2H, m), 6.96 (1H, d, J = 8.2 Hz), 7.24-7.39 (2H, m), 7.35- 7.47 (2H, m), 7.52 (1H, dd, J = 2.2, 8.2 Hz), 7.59 (1H, d, J = 2.0 Hz), 8.92 (2H, s), 10.21 (1H, s). 271  7.08 (1H, dd, J = 0.6, 8.2 Hz), 7.19-7.34 (3H, m), 7.42-7.52 (2H, m), 7.68-7.80 (2H, m), 8.21 (1H, s), 8.71 (2H, s). 272  3.58 (2H, s), 6.94 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 7.9, 1.0 Hz), 7.21-7.40 (4H, m), 7.43-7.52 (2H, m), 8.08-8.23 (1H, m), 8.66 (2H, s). 273  3.44 (2H, s), 3.99 (3H, s), 6.87-6.98 (2H, m), 7.22-7.35 (4H, m), 7.40-7.50 (2H, m), 7.93 (1H, s), 8.20 (1H, s). 274  3.60 (2H, s), 3.99 (3H, s), 6.89-6.96 (1H, m), 7.20-7.29 (3H, m), 7.29-7.39 (2H, m), 7.40- 7.49 (2H, m), 7.85 (1H, s), 8.21 (1H, s). 275  4.19 (3H, s), 7.22-7.35 (3H, m), 7.42- 7.54 (3H, m), 8.04 (1H, s), 8.15 (1H, d, J = 8.3 Hz), 9.28 (2H, s). 276  4.19 (3H, s), 7.19-7.39 (4H, m), 7.51 (1H, d, J = 8.3 Hz), 8.04 (1H, s), 8.16 (1H, d, J = 8.3 Hz), 9.28 (2H, s). 277  4.20 (3H, s), 6.96-7.11 (3H, m), 7.37- 7.48 (1H, m), 7.52 (1H, d, J = 8.3 Hz), 8.04 (1H, s), 8.17 (1H, d, J = 8.3 Hz), 9.29 (2H, s).








(243) TABLE-US-00041 TABLE 2-29 EX STR Prop DATA 278 0  embedded image 1 NMR2; 4.19 (3H, s), 7.09-7.23 (2H, m), 7.19- 7.27 (2H, m), 7.51 (1H, d, J = 8.3 Hz), 8.04 (1H, s), 8.16 (1H, d, J = 8.3 Hz), 9.28 (2H, s). 279  embedded image 1 NMR2; 7.20-7.28 (2H, m), 7.28-7.36 (1H, m), 7.43-7.53 (2H, m), 7.60 (1H, dd, J = 9.5, 1.6 Hz), 8.07 (1H, dd, J = 9.5, 1.1 Hz), 8.28-8.34 (1H, m), 8.78 (2H, s). 280  embedded image 1 NMR2; 7.19-7.37 (4H, m), 7.61 (1H, dd, J = 9.5, 1.6 Hz), 8.08 (1H, dd, J = 9.6, 1.2 Hz), 8.30-8.35 (1H, m), 8.78 (2H, s). 281  embedded image 1 NMR2; 7.19-7.37 (4H, m), 7.61 (1H, dd, J = 9.5, 1.6 Hz), 8.08 (1H, dd, J = 9.6, 1.2 Hz), 8.30-8.35 (1H, m), 8.78 (2H, s). 282  embedded image 1 NMR2; 6.96-7.09 (3H, m), 7.44 (1H, td, J = 8.3, 6.5 Hz), 7.61 (1H, dd, J = 9.5, 1.6 Hz), 8.08 (1H, dd, J = 9.6, 1.1 Hz), 8.29-8.35 (1H, m), 8.80 (2H, s). 283  embedded image 1 NMR2; 6.75 (1H, dd, J = 7.4, 1.8 Hz), 7.20- 7.34 (3H, m), 7.42-7.52 (2H, m), 7.55 (1H, s), 7.58- 7.64 (1H, m), 8.05 (1H, dt, J = 7.3, 1.1 Hz), 8.17 (1H, s), 8.78 (2H, s). 284  embedded image 1 NMR2; 6.76 (1H, dd, J = 7.3, 1.8 Hz), 6.96- 7.09 (3H, m), 7.36-7.47 (1H, m), 7.56 (1H, s), 7.60- 7.66 (1H, m), 8.06 (1H, dt, J = 7.3, 1.1 Hz), 8.18 (1H, s), 8.79 (2H, s). 285  embedded image 1 NMR2; 7.09 (1H, dd, J = 9.4, 1.4 Hz), 7.20- 7.28 (2H, m), 7.28-7.34 (1H, m), 7.43-7.53 (2H, m), 7.62 (1H, d, J = 1.0 Hz), 7.72 (1H, dd, J = 9.4, 1.1 Hz), 8.23 (1H, s), 8.76 (2H, s). 286  embedded image 1 NMR2; 7.10 (1H, dd, J = 9.4, 1.5 Hz), 7.18- 7.37 (4H, m), 7.62 (1H, d, J = 1.0 Hz), 7.73 (1H, dd, J = 9.4, 1.2 Hz), 8.24 (1H, s), 8.76 (2H, s). 287  embedded image 1 NMR2; 6.97-7.08 (3H, m), 7.10 (1H, dd, J = 9.4, 1.5 Hz), 7.43 (1H, tdd, J = 8.2, 6.5, 0.7 Hz), 7.62 (1H, d, J = 0.9 Hz), 7.74 (1H, dd, J = 9.4, 1.2 Hz), 8.25 (1H, s), 8.78 (2H, s). 288 0  embedded image 1 NMR2; 7.09 (1H, dd, J = 9.4, 1.5 Hz), 7.10- 7.26 (4H, m), 7.62 (1H, d, J = 0.9 Hz), 7.73 (1H, dd, J = 9.4, 1.2 Hz), 8.24 (1H, s), 8.76 (2H, s).


(244) TABLE-US-00042 TABLE 2-30 EX STR Prop DATA 289  embedded image 1 NMR2; 7.21-7.29 (2H, m), 7.29-7.37 (1H, m), 7.43-7.55 (3H, m), 8.29 (1H, dd, J = 9.7, 0.8 Hz), 9.16 (2H, s), 9.19 (1H, d, J = 0.8 Hz). 290  embedded image 1 NMR2; 7.20-7.38 (4H, m), 7.53 (1H, d, J = 9.7 Hz), 8.29 (1H, dd, J = 9.7, 0.8 Hz), 9.16 (2H, s), 9.20 (1H, d, J = 0.8 Hz). 291  embedded image 1 NMR2; 6.97-7.10 (3H, m), 7.40-7.48 (1H, m), 7.52 (1H, d, J = 9.7 Hz), 8.30 (1H, dd, J = 9.7, 0.8 Hz), 9.17 (2H, s), 9.20 (1H, d, J = 0.8 Hz). 292  embedded image 1 NMR2; 7.11-7.26 (4H, m), 7.51 (1H, d, J = 9.7 Hz), 8.29 (1H, dd, J = 9.7, 0.8 Hz), 9.16 (2H, s), 9.20 (1H, d, J = 0.8 Hz). 293  embedded image 1 NMR2; 7.21-7.29 (2H, m), 7.29-7.37 (1H, m), 7.44-7.54 (2H, m), 8.60 (1H, s), 8.82 (2H, s), 8.98- 9.05 (2H, m). 294  embedded image 1 NMR2; 7.32 (1H, dd, J = 9.3, 1.8 Hz), 7.38- 7.47 (1H, m), 7.62 (1H, ddd, J = 8.3, 2.8, 1.4 Hz), 7.67-7.81 (3H, m), 8.32 (1H, dd, J = 1.9, 1.0 Hz), 8.55 (1H, dd, J = 4.7, 1.4 Hz), 8.62 (1H, d, J = 2.7 Hz), 8.76 (2H, s). 295  embedded image 1 NMR2; 6.56 (1H, t, J = 73.5 Hz), 7.03-7.09 (2H, m), 7.12 (1H, ddd, J = 8.3, 2.1, 1.1 Hz), 7.31 (1H, dd, J = 9.3, 1.9 Hz), 7.41-7.50 (1H, m), 7.67-7.80 (3H, m), 8.31 (1H, dd, J = 1.9, 1.0 Hz), 8.76 (2H, s). 296  embedded image 1 NMR2; 7.20-7.28 (2H, m), 7.29-7.36 (1H, m), 7.42-7.53 (2H, m), 7.83 (1H, dd, J = 5.3, 0.5 Hz), 8.98 (1H, d, J = 5.3 Hz), 9.30 (2H, s). 297  embedded image 1 NMR2; 7.19-7.28 (2H, m), 7.32 (1H, ddt, J = 7.9, 7.0, 1.1 Hz), 7.43-7.53 (2H, m), 7.68 (1H, dd, J = 5.2, 1.8 Hz), 7.86 (1H, dd, J = 1.8, 0.8 Hz), 8.80- 8.86 (3H, m). 298 0  embedded image 1 NMR2; 4.60 (2H, s), 7.18-7.37 (3H, m), 7.42- 7.58 (4H, m), 8.47-8.52 (1H, m), 8.76 (2H, s).





(245) TABLE-US-00043 TABLE 2-31 EX STR Prop DATA 299  embedded image 1 NMR; 7.20-7.28(2H, m), 7.28-7.35(1H, m), 7.43-7.53(2H, m), 7.62-7.69(1H, m), 7.81- 7.87(1H, m), 8.85(3H, s) 300  embedded image 1 NMR2; 7.21-7.35(3H, m), 7.42-7.52(2H, m), 7.58(1H, d, J = 5.0 Hz), 9.05(1H, d, J = 5.0 Hz), 9.57(2H, s). 301  embedded image 1 NMR2; 7.20-7.34(3H, m), 7.41-7.53(2H, m), 7.65-7.72(1H, m), 7.86(1H, d, J = 8.0 Hz), 7.94- 8.04(1H, m), 9.21(2H, s).


(246) TABLE-US-00044 TABLE 2-32 EX STR Prop DATA 302  embedded image 302 NMR2; 2.85 (2H, t, J = 6.7 Hz), 3.87 (2H, t, J = 6.7 Hz), 6.71-6.75 (1H, m), 6.60-6.85 (2H, m), 7.04- 7.08 (2H, m), 7.27-7.32 (3H, m), 7.57 (1H, br). 303  embedded image 302 NMR2; 2.84 (2H, t, J = 6.7 Hz), 3.86 (2H, t, J = 6.7 Hz), 7.00-7.06 (4H, m), 7.11-7.17 (1H, m), 7.22- 7.28 (2H, m), 7.32-7.39 (2H, m), 7.56 (1H, s). 304  embedded image 302 NMR1; 2.68 (2H, t, J = 6.7 Hz), 3.67 (2H, t, J =






6.7 Hz), 3.93 (2H, s), 7.16-7.20 (1H, m), 7.23-7.31 (8H, m), 10.33 (1H, s). 305  embedded image 305 NMR2; 2.83 (2H, t, J = 6.7 Hz), 3.86 (2H, t, J = 6.7 Hz), 3.97 (2H, s), 6.86-6.99 (3H, m), 7.20-7.28 (5H, m), 7.42 (1H, br). 306  embedded image 306 NMR2; 2.85 (2H, t, J = 6.7 Hz), 3.87 (2H, t, J = 6.7 Hz), 6.89-6.90 (1H, m), 6.93-6.99 (2H, m), 7.04-7.08 (2H, m), 7.28-7.37 (3H, m), 7.74 (1H, br). 307  embedded image 307 NMR2; 2.85 (2H, t, J = 6.7 Hz), 3.88 (2H, t, J = 6.7 Hz), 7.04-7.08 (2H, m), 7.18-7.21 (1H, m), 7.28-7.38 (3H, m), 7.38 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.9 Hz), 7.73 (1H, br). 308  embedded image 308 NMR2; 2.89 (2H, t, J = 6.7 Hz), 3.24 (3H, s), 3.80 (2H, t, J = 6.7 Hz), 6.69-6.75 (1H, m), 6.79-6.84 (2H, m), 7.04-7.08 (2H, m), 7.25-7.31 (3H, m). 309  embedded image 309 NMR2; 2.84 (2H, t, J = 6.7 Hz), 3.85 (2H, t, J = 6.7 Hz), 6.95-7.05 (2H, m), 7.07-7.29 (6H, m), 7.47 (1H, s). 310  embedded image 310 NMR1; 2.70 (2H, t, J = 6.9 Hz), 3.76 (2H, t, J = 6.7 Hz), 6.97-7.03 (2H, m), 7.05-7.12 (2H, m), 7.20-7.28 (2H, m), 7.30-7.36 (2H, m), 10.37 (1H, s). 311  embedded image 311 NMR2; 2.84 (2H, t, J = 6.7 Hz), 3.79 (3H, s), 3.86 (2H, t, J = 6.7 Hz), 6.58-6.64 (2H, m), 6.66-6.72 (1H, m), 7.01-7.07 (2H, m), 7.21-7.28 (3H, m), 7.56 (1H, br).


(247) TABLE-US-00045 TABLE 2-33 EX STR Prop DATA 312  embedded image 312 NMR2; 2.85 (2H, t, J = 6.6 Hz), 3.89 (2H, t, J = 6.8 Hz), 6.90-6.96 (1H, m), 6.96-7.02 (1H, m), 7.09 (1H, ddd, J = 1.0, 1.6, 7.9 Hz), 7.23-7.32 (3H, m), 7.40-7.45 (2H, m), 7.52 (1H, br). 313



 embedded image 313 NMR2; 2.83 (2H, t, J = 6.7 Hz), 3.86 (2H, t, J = 6.7 Hz), 7.20-7.25 (2H, m), 7.25-7.36 (5H, m), 7.36-7.41 (2H, m), 7.49 (1H, br). 314  embedded image 314 NMR2; 2.85 (2H, t, J = 6.7 Hz), 3.87 (2H, t, J = 6.7 Hz), 6.51 (1H, t, J = 73.6 Hz), 6.80 (1H, dd, J = 2.2, 2.2 Hz), 6.84-6.91 (2H, m), 7.03-7.09 (2H, m), 7.27-7.35 (3H, m), 7.51 (1H, br). 315  embedded image 315 NMR2; 2.82 (2H, t, J = 6.7 Hz), 3.85 (2H, t, J = 6.7 Hz), 6.86 (1H, ddd, J = 0.8, 2.4, 8.3 Hz), 6.93 (1H, dd, J = 2.2, 2.2 Hz), 6.98-7.09 (5H, m), 7.34 (1H, dd, J = 8.1, 8.1 Hz), 7.56 (1H, br). 316  embedded image 316 NMR2; 2.84 (2H, t, J = 6.7 Hz), 3.89 (2H, t, J = 6.7 Hz), 6.95 (1H, ddd, J = 0.8, 0.8, 8.3 Hz), 7.02 (1H, ddd, J = 0.9, 5.0, 7.2 Hz), 7.15-7.22 (2H, m), 7.30-7.36 (2H, m), 7.59 (1H, br), 7.71 (1H, ddd, J = 2.0, 7.2, 8.3 Hz), 8.20 (1H, ddd, J = 0.7, 2.0, 5.0 Hz). 317


 embedded image 317 NMR2; 2.86 (2H, t, J = 6.7 Hz), 3.89 (2H, t, J = 6.7 Hz), 7.00-7.06 (2H, m), 7.07-7.13 (2H, m), 7.30-7.37 (2H, m), 7.53 (1H, br), 7.69-7.75 (2H, m). 318 0



 embedded image 318 NMR1; 2.71 (2H, t, J = 6.7 Hz), 3.78 (2H, t, J = 6.7 Hz), 7.07-7.12 (2H, m), 7.35-7.40 (2H, m), 7.43-7.46 (2H, m), 8.36-8.42 (2H, m), 10.39 (1H, s). 319


 embedded image 319 NMR2; 2.83 (2H, t, J = 6.6 Hz), 3.87 (2H, t, J = 6.7 Hz), 7.21-7.30 (2H, m), 7.30-7.39 (2H, m), 8.16 (1H, s). 320  embedded image 320 NMR2; 2.86 (2H, t, J = 6.7 Hz), 3.85 (2H, t, J = 6.7 Hz), 6.95 (1H, dd, J = 8.8, 0.6 Hz), 7.11-7.18 (2H, m), 7.19-7.25 (1H, m), 7.36-7.47 (2H, m), 7.69 (1H, dd, J = 8.8, 2.8 Hz), 7.78 (1H, s), 8.11 (1H, dd, J = 2.8, 0.7 Hz). 321


 embedded image 321 NMR2; 2.85 (2H, t, J = 6.7 Hz), 3.90 (2H, t, J = 6.7 Hz), 6.61-6.66 (1H, m), 6.76-6.81 (1H, m), 7.17-7.22 (2H, m), 7.31-7.36 (2H, m), 7.46 (1H, br), 7.78 (1H, dd, J = 8.0 Hz, 16.0 Hz).


(248) TABLE-US-00046 TABLE 2-34 EX STR Prop DATA 322  embedded image 322 NMR1; 5.69 (1H, d, J = 7.6 Hz), 6.99-7.13 (4H, m), 7.15-7.26 (3H, m), 7.39-7.49 (2H, m), 7.52 (1H, d, J = 7.7 Hz), 11.25 (1H, s). 323  embedded image 323 NMR2; 2.23 (3H, s), 2.75-2.93 (2H, m), 3.58-3.69 (1H, m), 3.80 (1H, ddd, J = 12.7, 8.2, 6.4 Hz), 6.83-6.88 (1H, m), 6.91 (1H, d, J = 2.8 Hz), 7.00-7.09 (2H, m), 7.09-7.19 (2H, m), 7.31-7.42 (2H, m), 7.58 (1H, s). 324



 embedded image 324 NMR2; 2.81 (2H, t, J = 6.7 Hz), 3.69 (2H, s), 3.80 (3H, s), 6.54 (1H, dd, J = 8.6, 2.6 Hz), 6.67 (1H, d, J = 2.5 Hz), 7.02-7.10 (2H, m), 7.11-7.21 (2H, m), 7.32-7.42 (2H, m), 7.68 (1H, s). 325

 embedded image 325 NMR2; 2.27 (3H, d, J = 0.7 Hz), 2.81-2.90 (2H, m), 3.65 (1H, dt, J = 12.6, 6.3 Hz), 3.81 (1H, ddd, J = 12.6, 7.9, 6.3 Hz), 6.82 (1H, t, J = 0.7 Hz), 7.09-7.18 (2H, m), 7.19-7.25 (1H, m), 7.36-7.46 (2H, m), 7.78 (1H, s), 8.01 (1H, s). 326  embedded image 326 NMR2; 2.39 (3H, s), 2.82-2.91 (2H, m), 3.66 (1H, t, J = 6.2 Hz), 3.71-3.83 (1H, m), 6.69 (1H, d, J = 8.5 Hz), 7.12-7.18 (2H, m), 7.18-7.25 (1H, m), 7.36-7.43 (2H, m), 7.47 (2H, d, J = 8.5 Hz). 327


 embedded image 327 NMR1; 2.73 (2H, t, J = 6.7 Hz), 3.84 (2H, t, J = 6.7 Hz), 7.34-7.40 (1H,

m), 7.40-7.45 (2H, m), 7.45-7.51 (2H, m), 7.65-7.72 (4H, m), 10.41 (1H, br). 328 0  embedded image 328 NMR2; 1.32 (3H, d, J = 6.6 Hz), 2.61 (1H, ddd, J = 0.8 Hz, 3.6 Hz, 16.6 Hz), 3.05 (1H, dd, J = 6.0 Hz, 16.6 Hz), 3.98-4.07 (1H, m), 7.01-7.08 (4H, m), 7.12-7.18 (1H, m), 7.19-7.25 (2H, m), 7.33- 7.40 (2H, m), 7.48 (1H, br). 329  embedded image 302 NMR1; 2.72 (2H, t, J = 6.6 Hz), 3.82 (2H, t, J = 6.6 Hz), 6.94-7.03 (2H, m), 7.09-7.16 (1H, m), 7.16- 7.25 (2H, m), 7.34-7.42 (2H, m). 7.42-7.50 (1H, m), 10.47 (1H, s). 330  embedded image 302 NMR1; 2.68-2.77 (2H, m), 3.85 (2H, t, J = 6.6 Hz), 6.92-7.01 (2H, m), 7.07-7.16 (1H, m), 7.32- 7.44 (4H, m), 10.56 (1H, s).

(249) TABLE-US-00047 TABLE 2-35 EX STR Prop DATA 331  embedded image 302 NMR1; 2.72 (2H, t, J = 6.7 Hz), 3.78 (2H, t, J = 6.7 Hz), 7.17 (1H, dd, J = 8.7, 0.7 Hz), 7.21-7.42 (4H, m), 7.87 (1H, dd, J = 8.8, 2.7 Hz), 8.08 (1H, dd, J = 2.8, 0.7 Hz), 10.48 (1H, s). 332  embedded image 302 NMR1; 2.73 (2H, t, J = 6.7 Hz), 3.80 (2H, t, J = 6.7 Hz), 6.99 (1H, ddd, J = 8.2, 2.1, 0.9 Hz), 7.04-7.11 (2H, m), 7.13 (1H, dd, J = 8.7, 0.6 Hz), 7.40-7.51 (1H, m), 7.88 (1H, dd, J = 8.7, 2.8 Hz), 8.16 (1H, dd, J = 2.8, 0.7 Hz), 10.49 (1H, s). 333  embedded image 302 NMR1; 2.72 (2H, t, J = 6.6 Hz), 3.79 (2H, t, J = 6.7 Hz), 7.18 (1H, dd, J = 8.7, 0.6 Hz), 7.44-7.51 (1H, m), 7.51-7.56 (1H, m), 7.57-7.63 (1H, m), 7.63- 7.72 (1H, m), 7.90 (1H, dd, J = 8.8, 2.8 Hz), 8.15 (1H, dd, J = 2.8, 0.6 Hz), 10.49 (1H, s). 334  embedded image 302 NMR2; 2.25 (3H, s), 2.76-2.94 (2H, m), 3.65 (1H, dt, J = 12.6, 6.1 Hz), 3.81 (1H, ddd, J = 12.7, 8.2, 6.4 Hz), 6.74 (1H, dt, J = 10.1, 2.4 Hz), 6.79-6.86 (2H, m), 6.87-6.92 (1H, m), 6.92-6.97 (1H, m), 7.16 (1H, d, J = 8.5 Hz), 7.30 (1H, td, J = 8.3, 6.6 Hz), 7.56 (1H, s). 335  embedded image 302 NMR2; 2.26 (3H, s), 2.77-2.94 (2H, m), 3.66 (1H, dt, J = 12.5, 6.1 Hz), 3.82 (1H, ddd, J = 12.7, 8.3, 6.4 Hz), 6.89 (1H, ddd, J = 8.6, 2.9, 0.6 Hz), 6.94 (1H, dd, J = 2.7, 0.7 Hz), 7.14-7.23 (2H, m), 7.27-7.32 (1H, m), 7.35-7.42 (1H, m), 7.42- 7.50 (1H, m), 7.62 (1H, s). 336  embedded image 302 NMR2; 2.26 (3H, s), 2.76-2.92 (2H, m), 3.65 (1H, dt, J = 12.5, 6.1 Hz), 3.82 (1H, ddd, J = 12.7, 8.3, 6.3 Hz), 6.85-7.03 (5H, m), 7.17 (1H, d, J = 8.5 Hz), 7.35 (1H, t, J = 8.2 Hz), 7.73 (1H, s). 337  embedded image 337 NMR2; 1.31 (6H, s), 2.74 (2H, s), 6.99-7.05 (2H, m), 7.05-7.10 (2H, m), 7.11-7.20 (3H, m), 7.34- 7.42 (2H, m), 7.52 (1H, br). 338 0  embedded image 305 NMR2; 2.82 (2H, t, J = 6.7 Hz), 3.85 (2H, t, J = 6.7 Hz), 3.95 (2H, s), 6.94-7.01 (2H, m), 7.10-7.17 (2H, m), 7.18-7.24 (4H, m), 7.43 (1H, br). 339  embedded image 305 NMR2; 2.83 (2H, t, J = 6.7 Hz), 3.86 (2H, t, J = 6.7 Hz), 4.00 (2H, s), 7.02-7.14 (3H, m), 7.19-7.28 (4H, m), 7.31 (1H, dd, J = 7.9, 7.9 Hz), 7.43 (1H, br).

(250) TABLE-US-00048 TABLE 2-36 EX STR Prop DATA 340  embedded image 305 NMR2; 2.82(2H, t, J = 6.7 Hz), 3.86(2H, t, J = 6.7 Hz), 3.98(2H, s), 7.11-7.16(2H, m), 7.17- 7.25(6H, m), 7.47(1H, br). 341  embedded image 305 NMR2; 2.83(2H, t, J = 6.7 Hz), 3.86(2H, t, J = 6.7 Hz), 4.04(2H, s), 7.19-7.27(4H, m), 7.34- 7.51(5H, m). 342  embedded image 305 NMR2; 2.83(2H, t, J = 6.7 Hz), 3.86(2H, t, J = 6.7 Hz), 4.04(2H, s), 7.18-7.27(4H, m), 7.30(2H, d, J = 7.9 Hz), 7.49(1H, br), 7.55(2H, d, J = 8.0 Hz). 343  embedded image 343 NMR2; 0.91(3H, t, J = 7.5 Hz), 1.60-1.73(1H, m), 1.74-1.87(1H, m), 2.76(1H, ddd, J = 0.9, 2.8, 16.7 Hz), 3.01(1H, ddd, J = 0.5, 6.4, 16.7 Hz), 3.75-3.83(1H, m), 7.00-7.08(4H, m), 7.12- 7.18(1H, m), 7.21-7.28(2H, m), 7.33-7.41(2H, m), 7.46(1H, br). 344  embedded image 344 NMR2; 2.88(2H, t, J = 6.7 Hz), 3.89(2H, t, J = 6.7 Hz), 6.48-6.60(3H, m), 7.06-7.13(2H, m), 7.30-7.36(2H, m), 7.51(1H, br). 345  embedded image 302 NMR2; 2.87-3.08(2H, m), 3.79-3.97(2H, m), 6.78-6.90(3H, m), 6.98(1H, d, J = 8.1 Hz), 7.32(1H, ddd, J = 6.6 Hz, 8.3 Hz, 8.3 Hz), 7.37 (1H, d, J = 8.0 Hz), 7.54-7.67(3H, m), 7.78-7.83(1H, m), 8.23-8.29(1H, m). 346  embedded image 346 NMR2; 5.82(1H, d, J = 8.0 Hz), 7.20-7.34(3H, m), 7.43-7.53(2H, m), 7.93(1H, d, J = 8.0 Hz), 8.49- 8.55(2H, m), 11.65(1H, s). 347  embedded image 347 NMR2; 2.84(2H, t, J = 6.7 Hz), 4.32(2H, t, J = 6.7 Hz), 7.16-7.35(4H, m), 7.38-7.50(2H, m), 7.54(1H, s), 8.13(1H, d, J = 9.5 Hz).

(251) TABLE-US-00049 TABLE 2-37 EX STR Prop DATA 348 0  embedded image 1 NMR2; 7.21-7.26(2H, m), 7.29-7.35(1H, m), 7.45-7.52(2H, m), 7.68(1H, dd, J = 5.1, 1.8 Hz), 7.86(1H, dd, J = 1.8, 0.7 Hz), 8.80-8.85(3H, m). 349  embedded image 1 NMR2; 7.22-7.27(2H, m), 7.28-7.34(1H, m), 7.45-7.51(2H, m), 7.80(1H, dd, J = 8.3, 0.8 Hz), 8.06(1H, dd, J = 8.3, 2.2 Hz),

8.96(1H, d, J = 2.2, 0.8 Hz), 9.21(2H, s). 350  NMR2; 7.22-7.28(2H, m), 7.28-7.34(1H, m), 7.43-7.51(2H, m), 7.70(1H, dd, J = 7.5, 1.0 Hz), 7.89(1H, dd, J = 8.2, 1.0 Hz), 7.96(1H, dd, J = 8.2, 7.5 Hz), 9.18(2H, s).

## Test Examples

(252) Pharmacological test results for typical compounds of the present invention are given below and the pharmacological actions of these compounds are explained, but the present invention is not limited by these test examples.

### [Test Example 1] Audiogenic Seizure Model

(253) The animal model used in this test is a phenotype model for partial seizure (including secondary generalized seizure) and generalized tonic-clonic seizure, and has high clinical predictability. This test was performed in accordance with the report of De Sarro et al (Br J Pharmacol. 1988 February; 93 (2): 247-56. Anticonvulsant effects of some calcium entry blockers in DBA/2 mice. De Sarro G B, Meldrum B S, Nistico G.).

(254) In this test example, the example compounds shown in Tables 3-1 to 3-3 below were used as test compounds.

(255) The test compounds were suspended in 5% gum arabic/distilled water (w/v), and administered by forced oral administration to male and female DBA/2 mice (Japan SLC, Inc., 3 weeks old, 8 per group) at a dose of 30 mg/kg. After one hour of the oral administration of the test compound, each mouse was placed in a transparent acrylic cylinder 30 cm high and 23 cm in diameter, and 30 seconds were allowed for habituation. Then, they were exposed to auditory stimulation (12.6 kHz, 100-110 dB) for 1 minute or until a tonic seizure occurred.

(256) The seizure response was assessed using the following scale, 0: no seizure, 1: wild running, 2: clonic seizure, 3: tonic seizure and 4: respiratory arrest. The maximum response was recorded as the seizure severity score.

(257) The seizure suppression rate for each compound administration group was calculated according to the following formula.

$$(258) \text{ seizure suppression rate (\%)} = \left(1 - \frac{\text{seizure severity score of compound administration group}}{\text{seizure severity score of solvent administration group}}\right) \times 100 \quad [\text{Math.1}]$$

(259) The results are shown in Tables 3-1 to 3-3.

(260) Here, a rate of seizure suppression of 90% or more was expressed as “A”, a rate of seizure suppression of 70% or more and less than 90% was expressed as “B”, and a rate of seizure suppression of 50% or more and less than 70% was expressed as “C”.

(261) TABLE-US-00050 TABLE 3-1 Dose Seizure EX (mg/kg) suppression 1 5 A 2 30 A 3 5 A 4 5 A 5 5 A 6 5 A 7 5 A 8 10 A 9 5 A 10 30 A 11 5 A 12 3 A 13 3 A 14 30 A 15 30 A 16 30 A 17 30 A 18 30 A 19 30 A 20 30 A 21 30 A 22 5 A 23 30 A 24 5 A 25 30 A 26 5 A 27 30 A 28 30 A 29 30 A 30 5 A 31 5 A 32 30 A 33 5 A 34 30 A 35 30 A 36 5 A 37 30 A 38 10 A 39 30 A 40 3 A 41 30 A 42 5 A 43 30 A 44 30 A 45 5 A 46 30 A 47 30 A 48 30 A 49 30 A 50 30 A 51 30 A 52 30 A 53 30 A 54 30 A 55 30 A 56 30 A 57 30 A 58 30 A 59 3 A 60 30 A 61 30 A 62 30 A 63 30 A 64 3 A 65 30 A 66 30 A 67 30 A 68 30 A 69 30 A 70 30 A 71 30 A 72 30 A 73 30 A 74 5 A 75 30 A 76 30 A 77 30 A 78 30 A 79 30 A 80 30 A 81 30 A 82 30 A 83 30 A 84 30 A 85 30 A 86 30 A 87 30 A 88 30 A 89 30 A 90 5 B 91 5 A 92 5 A 93 30 A 94 30 A 95 3 A 96 30 A 97 3 A 98 3 A 99 10 A 100 30 A 101 3 A 102 10 A 103 30 A 104 30 A 105 30 A 106 5 A 107 30 A 108 30 A 109 30 A 110 30 A 111 30 A 112 30 A 113 10 A 114 5 A 115 30 A 116 30 A 117 30 A 118 5 B 119 5 A 120 5 A

(262) TABLE-US-00051 TABLE 3-2 Dose Seizure EX (mg/kg) suppression 121 5 A 122 5 A 123 5 A 124 30 A 125 30 A 126 30 A 127 5 A 128 30 A 129 5 A 130 30 A 131 30 A 132 30 A 133 30 A 134 5 A 135 30 A 136 30 A 137 30 A 138 30 A 139 30 A 140 30 A 141 5 A 142 30 A 143 30 A 144 30 A 145 30 A 146 30 A 147 30 A 148 30 A 149 30 A 150 30 A 151 5 A 152 30 A 153 30 A 154 30 A 155 5 A 156 30 A 157 30 A 158 30 A 159 30 A 160 30 A 161 5 A 162 5 A 163 5 A 164 5 A 165 5

A 166 5 A 167 5 A 168 5 A 169 5 A 170 5 A 171 5 A 172 5 A 173 5 A 174 30 A 175 30 A 176 30 A 177 5 B 178 30 A 179 30 A 180 30 A 181 5 B 182 30 A 183 30 A 184 5 A 185 30 A 186 30 A 187 30 A 188 30 A 189 30 A 190 5 A 191 30 A 192 30 A 193 30 A 194 5 A 195 30 A 196 30 A 197 30 A 198 5 A 199 30 A 200 30 A 201 30 A 202 30 A 203 30 A 204 30 A 205 30 A 206 30 A 207 30 A 208 30 A 209 30 A 210 30 A 211 30 A 212 30 A 213 30 A 214 30 A 215 30 A 216 5 A 217 30 A 218 30 A 219 30 A 220 30 A 221 30 A 222 30 A 223 30 A 224 30 A 225 30 A 226 5 A 227 30 A 228 30 A 229 30 A 230 30 A 231 30 A 232 30 A 233 30 A 234 30 A 235 30 A 236 30 A 237 30 A 238 30 A 239 30 A 240 30 A

(263) TABLE-US-00052 TABLE 3-3 Dose Seizure EX (mg/kg) suppression 241 30 A 242 30 A 243 5 A 244 30 A 245 30 A 246 30 A 247 30 A 248 5 A 249 30 A 250 30 A 251 30 A 252 30 A 253 30 A 254 30 A 255 30 A 256 5 B 257 30 A 258 5 A 259 5 A 260 30 A 261 30 A 262 5 A 263 30 A 264 30 A 265 30 A 266 30 A 267 5 A 268 30 A 269 30 A 270 30 A 271 30 A 272 30 A 273 30 A 274 30 A 275 30 A 276 30 A 277 30 A 278 30 A 279 1 A 280 30 A 281 30 A 282 30 A 283 5 A 264 5 A 285 5 A 286 30 A 287 30 A 288 30 A 289 1 A 290 30 A 291 30 A 292 30 A 293 30 A 294 5 A 295 5 A 296 30 A 297 1 A 298 1 A 299 5 A 300 30 A 301 30 A 302 30 A 303 30 A 304 30 A 305 30 A 806 30 A 307 30 B 308 30 C 309 30 A 310 30 C 311 30 B 312 30 C 313 30 C 314 30 A 315 30 B 316 30 A 317 30 C 318 30 C 319 30 C 320 30 A 321 30 C 322 30 C 323 39 B 324 30 C 325 30 B 326 30 C 327 30 C 328 30 A 329 30 B 330 30 C 331 30 B 332 30 B 333 30 C 334 30 C 335 30 B 336 30 B 337 30 A 338 30 C 339 30 B 340 30 B 341 30 C 342 30 C 343 30 A 344 30 C 345 30 C 346 30 C 347 30 A 348 1 A 349 3 A 350 10 A

[Test Example 2] Rotarod Test

(264) This test is performed to evaluate the effect of the compound on the motor coordination.

(265) In this test example, the example compounds shown in Table 4 below were used as test compounds.

(266) Male ICR mice (Japan SLC, Inc., 5-6 weeks, 8 per group) were trained to remain on a fixed speed (15 rpm) rotating rod of rotarod apparatus (Muromachi Kikai Co., Ltd.) for 2 minutes. The test compound was suspended in 5% gum arabic/distilled water (w/v), and administered by forced oral administration at a dose of 30 mg/kg. After 1 hour of oral administration, the mice were again placed on the rod accelerated from 4 rpm to 40 rpm over 5 minutes and the latency to fall off the rod was recorded for 200 seconds. The falling latency of the compound administration group was calculated as a relative value relative to the average value of the falling latency in the solvent administration group.

(267) The results are shown in Tables 4-1 and 4-2.

(268) Here, a coordination disorder of 25% or less was expressed as “A”, and a coordination disorder of more than 25% and 50% or less was expressed as “B”.

(269) TABLE-US-00053 TABLE 4-1 Dose Motor EX (mg/kg) dysfunction 1 5 A 2 10 A 3 10 A 4 5 A 5 5 A 6 5 A 7 5 A 8 10 A 10 30 A 11 5 A 22 5 A 24 5 A 26 5 A 27 30 A 30 5 A 31 5 A 33 30 A 34 30 A 36 5 A 38 10 A 40 3 A 42 5 A 55 30 A 58 30 A 59 3 A 64 3 A 66 30 A 74 5 A 90 5 A 91 5 A 92 5 A 93 30 A 95 10 A 97 3 A 98 3 A 99 10 A 101 3 A 102 10 A 103 30 A 107 30 A 113 10 A 114 5 A 118 5 A 119 5 A 120 5 B 121 5 A 122 5 A 123 5 A 127 5 B 129 5 A 134 5 B 137 30 A 141 5 B 143 30 A 148 30 A 151 5 A 155 5 A 161 5 A 162 5 A 163 5 A 170 5 A 171 5 A 172 5 A 173 5 A 177 5 A 181 5 A 184 5 A 188 30 A 190 5 A 194 5 A 198 5 A 204 5 A 211 30 B 214 30 A 216 5 A 220 30 A 222 30 A 223 30 A 224 30 A 226 5 B 229 30 A 235 30 A 236 30 A 237 30 A 239 30 A 243 5 A 245 30 A 248 5 A 256 5 A 258 5 A 259 5 A 262 5 A 267 5 A 275 30 A 279 1 A 283 5 A 285 5 A 289 1 A 293 30 A 294 5 A 295 5 A 296 30 A 297 1 A 298 1 A 299 5 A 300 30 A 302 30 A 303 30 A 304 30 A 305 30 A 306 30 A

(270) TABLE-US-00054 TABLE 4-2 Dose Motor EX (mg/kg) dysfunction 307 30 A 309 30 A 311 30 A 314 30 A 316 30 A 320 30 B 323 30 B 325 30 A 328 30 A 329 30 A 331 30 A 332 30 A 336 30 A 337 30 A 340 30 A 343 30 A 347 30 A 348 1 A 349 3 A 350 10 A

[Test Example 3] Maximal Electroshock Seizure (MES) Model

(271) This test is performed to evaluate the anticonvulsant activity of the compound. The mouse model used in this test is a phenotype model of generalized tonic-clonic seizure and secondary generalized partial seizure. This test was performed in accordance with the report of AJ Hill et al (Br J Pharmacol. 2012 December; 167 (8): 1629-42. Cannabidivarin is anticonvulsant in mouse and rat, Hill A J, et al.).

(272) The test compound is suspended in 5% gum arabic/distilled water (w/v), and administers by forced oral administration to male ICR mice (Japan SLC, Inc., 5 to 6 weeks old, 8 per group) at a dose of 30 mg/kg. After one hour of the oral administration of the test compound, the mice are stimulated by an application of electrical current (30 mA, 100 Hz, 0.2 second) through auricular electrodes using an electroconvulsive device (UGO BASILE SRL). Then, the incidence of tonic hindlimb extension seizure is recorded.

(273) In the above test, it is confirmed that, in the solvent administration group, tonic hindlimb extension seizure is induced in all examples, but in the test compound administration group, expression of seizure is suppressed.

[Test Example 4] Subcutaneous Pentylenetetrazole (scPTZ) Model

(274) This test is performed to evaluate the anticonvulsant activity of the compound as in Test Example 3. Unlike the phenotype of Test Example 3, the animal model used in this test is a phenotype model of generalized absence seizure and myoclonic seizure.

(275) The test compound is suspended in 5% gum arabic/distilled water (w/v), and administers by forced oral administration to male ICR mice (Japan SLC, Inc., 5 to 6 weeks old, 10 per group) at a dose of 30 mg/kg. After 1 hour, 85 mg/kg of pentylenetetrazole dissolved in saline is administered subcutaneously, and the occurrence of clonic convulsions is evaluated for 30 minutes.

(276) In the above test, it is confirmed that, in the solvent administration group, clonic convulsion is induced in all examples, but in the test compound administration group, expression of convulsion is suppressed.

(277) Thus, since the compound of the present invention exhibits anticonvulsive action in all cases in multiple animal models used to evaluate antiepileptic drugs, it is useful as an antiepileptic drug with a wide treatment spectrum (compound for preventing and/or treating seizure in disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus)). Moreover, the compound of the present invention is useful as a diagnostic compound for disease involving epileptic seizure or convulsive seizure (including multiple drug resistant seizure, refractory seizure, acute symptomatic seizure, febrile seizure and status epilepticus).

## EXAMPLES

### Example 1

Synthesis of 3-Methoxy-6-(2-Phenoxy-5-pyrimidin-5-yl)pyridazine

(278) A mixture containing

(279) 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (5.00 g), 3-chloro-6-methoxypyridazine (3.64 g), PdCl<sub>2</sub>.sub.2 (dppf) DCM (0.137 g), K<sub>2</sub>CO<sub>3</sub>.sub.4 (7.12 g), 1,4-dioxane (50 mL), and water (25 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. The reaction solution was poured into water, and the product was extracted with AcOEt. The organic layer was washed with water and brine and dried with anhydrous sodium sulfate and then concentrated. The residue was purified through silica gel column chromatography (DCM/AcOEt) to obtain the object compound (4.42 g).

### Example 4

Synthesis of 3-(2-(3-Fluorophenoxy)pyrimidin-5-yl)-6-Methoxypyridazine

(280) A mixture containing 5-bromo-2-(3-fluorophenoxy)pyrimidine (2.234 g), (BPin).sub.2 (2.63 g), PdCl<sub>2</sub>.sub.2 (dppf) DCM (0.282 g), AcOK (1.358 g), and 1,4-dioxane (20 mL) was heated to reflux under a nitrogen atmosphere for 2 hours. 3-Chloro-6-methoxypyridazine (1.00 g), PdCl<sub>2</sub>.sub.2 (dppf) DCM (0.282 g), K<sub>2</sub>CO<sub>3</sub>.sub.4 (2.94 g), and water (5 mL) were added to the



reaction solution and the mixture was heated to reflux under a nitrogen atmosphere overnight. Water and AcOEt were added to the

## Claims

1. A compound represented by Formula I: ##STR00493## wherein D is ##STR00494## ring A is benzene; ring B is pyrimidine; ring C is the following unsaturated rings, oxides thereof, dioxides thereof, provided that pyrimidine-2,4-dione and dihydropyrimidine-2,4-dione are excluded, or those in which a part or all of unsaturated bonds in the unsaturated rings are reduced with hydrogen: pyridazine, pyrimidine, indole, pyrrolopyridine, indazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, triazolopyridine, pyrazolopyrimidine, imidazopyrimidine, triazolopyrimidine, isoquinoline, naphthyridine, quinazoline, quinoxaline, benzodioxole, oxazine, oxazepine, benzothiazole, and triazolopyridazine; wherein ring C is bonded to a 5-position of ring B, R.sup.1 is halogen, C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen or —CN; R.sup.2 is —O—C.sub.1-6 alkyl; R.sup.3 is halogen, C.sub.1-6 alkyl optionally substituted with halogen or —O—C.sub.1-6 alkyl, —O—C.sub.1-6 alkyl optionally substituted with halogen, —C.sub.1-6 alkyl-OH, —OH, —CN, —CONH.sub.2 or —NH.sub.2; L is —O—, which is bonded at a 2-position of ring B; and k is 0, 1 or 2, and when k is 2, each R.sup.1 independently represents the same or different substituent; m is 0 or 1; n is 0, 1 or 2, and when n is 2, each R.sup.3 independently represents the same or different substituent; or a salt thereof.
2. The compound according to claim 1, wherein, in Formula I, ring C is the following unsaturated rings, oxides thereof, or those in which a part or all of unsaturated bonds in the unsaturated rings are reduced with hydrogen: pyridazine, pyrrolopyridine, indazole, pyrazolopyridine, imidazopyridine, imidazopyrazine, imidazopyridazine, pyrazolopyrimidine, triazolopyrimidine, isoquinoline, naphthyridine, quinoxaline, triazolopyridine, and triazolopyridazine; R.sup.1 is halogen or C.sub.1-6 alkyl optionally substituted with halogen; R.sup.3 is C.sub.1-6 alkyl optionally substituted with halogen, —O—C.sub.1-6 alkyl optionally substituted with halogen, —OH, —CONH.sub.2 or —NH.sub.2; k and n are 0 or 1; and m is 0; or a salt thereof.
3. The compound according to claim 2, wherein, in Formula I, ring C is the following unsaturated rings, oxides thereof, or those in which a part or all of unsaturated bonds in the unsaturated rings are reduced with hydrogen: pyridazine, pyrazolopyridine, and imidazopyridine; R.sup.3 is —OH or —NH.sub.2; L is —O—; k and m are 0; and n is 0 or 1; or a salt thereof.
4. A compound selected from the group consisting of the following compounds: ##STR00495## ##STR00496## ##STR00497## ##STR00498## or a salt thereof.
5. The compound according to claim 4 selected from the group consisting of the following compounds: ##STR00499## ##STR00500## or a salt thereof.
6. A compound represented by the following formula: ##STR00501## or a salt thereof.
7. A compound represented by the following formula: ##STR00502## or a salt thereof.
8. A compound represented by the following formula: ##STR00503## or a salt thereof.
9. A compound represented by the following formula: ##STR00504## or a salt thereof.
10. A compound represented by the following formula: ##STR00505## or a salt thereof.
11. A compound represented by the following formula: ##STR00506## or a salt thereof.
12. A compound represented by the following formula: ##STR00507## or a salt thereof.
13. A compound represented by the following formula: ##STR00508## or a salt thereof.
14. A compound represented by the following formula: ##STR00509## or a salt thereof.
15. A compound represented by the following formula: ##STR00510## or a salt thereof.
16. A compound represented by the following formula: ##STR00511## or a salt thereof.
17. A compound represented by the following formula: ##STR00512## or a salt thereof.

