

P- 2022/12791

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIRECCIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **NC2022/0008012**Solicitud de patente a nombre de **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

Yo, CAROLINA DAZA MONTALVO identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, obrando como apoderada de la sociedad TAKEDA PHARMACEUTICAL COMPANY LIMITED., domiciliada en Osaka, Japón, respectivamente, solicitante de la patente de la referencia, en respuesta al oficio No. **11443** notificado electrónicamente el 23 de Julio de 2025, relacionado con los requerimientos de fondo de la solicitud, atentamente me permito presentar la siguiente información:

1. Título

El examinador afirma que el título de la invención "ANTAGONISTAS HETEROCÍCLICOS DE NMDA" no se relaciona con el objeto de la solicitud contenida en las reivindicaciones.

Para superar la objeción, el solicitante propone modificar el título tal como se muestra a continuación: "COMPUESTOS DE PIRROLIDIN-2-ONA, OXAZOLIDIN-2-ONA E IMIDAZOLIDIN-2-ONA COMO ANTAGONISTAS DEL NMDA".

2. Modificación al capítulo reivindicatorio:

Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto a este memorial un nuevo capítulo reivindicatorio que consta de cuarenta y tres (43) reivindicaciones, el cual reemplaza completamente el documento presentado el 30 de noviembre de 2022. Específicamente, se realizaron las siguientes modificaciones:

2.1. Se modificó la reivindicación independiente 1, con el fin de:

- 2.1.1.** Aclarar que la sal es una "*sal farmacológicamente aceptable*". Dicha modificación se sustenta en la página 24 línea 6 de la descripción.
- 2.1.2.** Reemplazar la expresión "*opcionalmente sustituido*" por "*no están sustituidos o están sustituidos*" en los radicales R^1 y R^2 y anillos A, anillo B^1 , B^2 y B^3 .
- 2.1.3.** Reclamar que los radicales R^1 y R^2 no están sustituidos o están sustituidos con "*uno a siete átomos de flúor*". Esto se soporta en la página 5 de la descripción líneas 33 a 35.
- 2.1.4.** Reclamar que los grupos benceno del anillo A no están sustituidos o están sustituidos con uno a cuatro halógenos además R^1 y -O-anillo B. Esta modificación se sustenta en la página 3 líneas 2-3 y pagina 19 líneas 13 a 16 de la descripción.
- 2.1.5.** Aclarar que los grupos del anillo B^1 están sustituidos con uno a cuatro halógenos. Dicha modificación se sustenta en la página 20, líneas 16 a 20 de la descripción.
- 2.1.6.** Reclamar que los grupos de los anillos B^2 y B^3 están sustituidos con uno a dos halógenos. Esta modificación se sustenta en la página 20, líneas 16 a 20 de la descripción.

2.2. Se modificó las reivindicaciones 2, 3 y 4, con el fin de:

- 2.2.1.** Indicar que la sal del compuesto 1 es "*farmacológicamente aceptable*". Esta modificación se sustenta en la página 24 líneas 6-7 de la descripción.
- 2.2.2.** Reemplazar el término "*flúor*" por "*átomos de flúor*".

- 2.3.** Se incluyó la nueva reivindicación 5, con el fin de reclamar un compuesto de la reivindicación 1 con las características de soportadas en las páginas 2 a 4 de la descripción.
- 2.4.** Se incluyó la nueva reivindicación 6, con el fin de reclamar los compuestos de la Tabla 1 de la descripción y sus sales farmacológicamente aceptables.
- 2.5.** Se modificaron las antiguas reivindicaciones 5, 8 y 9 (nuevas reivindicaciones 7, 21 y 31), con el fin de aclarar que la sal es una "*sal farmacológicamente aceptable*". Dicha modificación se sustenta en la página 24 línea 6 de la descripción.

- 2.6.** Se incluyeron las nuevas reivindicaciones 8 a 13, con el fin de reclamar el patrón de difracción de rayos X del compuesto reclamado en la antigua reivindicación 6 (nueva reivindicación 14). El sustento de dichas reivindicaciones se encuentra en el Ejemplo 17 de la descripción.
- 2.7.** Se incluyeron las nuevas reivindicaciones 15 a 19, con el fin de reclamar el patrón de difracción de rayos X del compuesto reclamado en la antigua reivindicación 7 (nueva reivindicación 20). El sustento de dichas reivindicaciones se encuentra en el Ejemplo 38 de la descripción.
- 2.8.** Se incluyeron las nuevas reivindicaciones 22 a 30, con el fin de reclamar el patrón completo de difracción de rayos X del compuesto reclamado en la antigua reivindicación 8 (nueva reivindicación 21). El sustento de dichas reivindicaciones se encuentra en el Ejemplo 45 de la descripción.
- 2.9.** Se incluyeron las nuevas reivindicaciones 32 a 39 con el fin de reclamar el patrón completo de difracción de rayos X del compuesto reclamado en la antigua reivindicación 9 (nueva reivindicación 31). El sustento de dichas reivindicaciones se encuentra en el Ejemplo 49 de la descripción.
- 2.10.** Se modificó la antigua reivindicación 10 (nueva reivindicación 40), de manera que dependa tanto de los compuestos como de las formas cristalinas de las reivindicaciones anteriores.
- 2.11.** Se incluyó la nueva reivindicación 41, con el fin de reclamar el proceso para preparar el compuesto de Fórmula (Ia). Esta reivindicación se sustenta en el *Método de producción A* reclamado en las páginas 44 y 45 de la descripción.
- 2.12.** Se incluyó la nueva reivindicación 42, con el fin de reclamar el proceso para preparar el compuesto (7). Esta reivindicación se sustenta en el *Método de producción A* reclamado en las páginas 44 y 45 de la descripción.
- 2.13.** En la nueva reivindicación 43, se reclama el proceso para preparar el compuesto de Fórmula (Ib). Esta reivindicación se sustenta en el *Método de producción B* reclamado en las páginas 45 y 46 de la descripción.
- 2.14.** Se eliminó la antigua reivindicación 11.

Estas modificaciones no amplían de ninguna manera la materia objeto de la presente solicitud, ya que se encuentran sustentadas en la descripción, y se realizan con el fin de definir la materia reclamada de forma clara y superar las objeciones planteadas por el examinador en su concepto técnico.

3. Pago de tasas

Considerando que el presente memorial se presenta junto con modificaciones a las reivindicaciones, se adjunta recibo por concepto de pago de tasa de modificación a la solicitud, según lo establecido en la **Resolución 59669 de 2020**.

Ahora, en relación con el número de reivindicaciones, atentamente me permito resaltar que junto a la presente respuesta se realiza el pago de la tasa por concepto de 32 reivindicaciones adicionales, dado que el nuevo capítulo reivindicatorio cuenta con un mayor número de cláusulas que el presentado y estudiado anteriormente por su despacho.

Por otra parte, es deseo del solicitante requerir que, si el examinador considera que aún existen motivos que impidan la concesión de la solicitud, proceda a emitir un nuevo examen de patentabilidad, para lo cual se anexa el respectivo pago de nuevo examen.

4. Claridad y concisión de las reivindicaciones

El solicitante manifiesta que mediante la presentación del nuevo capítulo reivindicatorio quedan subsanadas la totalidad de las objeciones presentadas por el examinador en su concepto técnico, de modo tal que las nuevas reivindicaciones reclaman de manera clara y concisa la invención descrita. Con respecto a las objeciones específicas del examinador, me permito manifestar lo siguiente:

- 4.1. El examinador considera que el conjunto de reivindicaciones 1 a 5 carecen de claridad, debido a que la referencia al término "*opcionalmente sustituido*", introduce características optativas que no permiten delimitar el alcance de la invención por sus características técnicas esenciales. Por ende, el examinador sugiere eliminar dicha referencia y especificar cuáles sustituciones son esenciales y cuáles no.

En este sentido, el solicitante manifiesta respetuosamente su desacuerdo con la opinión del examinador. No obstante, con el propósito de dar continuidad al procedimiento, el solicitante desea resaltar que las reivindicaciones fueron modificadas para sustituir el término opcional por "*no están sustituidas o están sustituidas*", como se puede ver en detalle en la sección 1 de este memorial.

Por ende, bajo esta nueva redacción, se establece de manera precisa el alcance estructural esencial de los radicales, incorporando en su alcance las distintas variantes o modalidades estructurales sin que el lenguaje empleado pueda considerarse ambiguo u optativo por parte del examinador. En este sentido, el solicitante respetuosamente solicita que la objeción al respecto se considere superada.

- 4.2.** Asimismo, el examinador considera que la reivindicación 1 carece de claridad, debido a que la expresión "*al menos*" resulta imprecisa, pues no permite diferenciar la invención frente al estado de la técnica. En consecuencia, el examinador recomienda eliminar esta referencia y definir un número exacto o un rango concreto para los átomos de flúor, asegurando una delimitación clara del alcance reivindicado.

El solicitante respetuosamente manifiesta su desacuerdo con la opinión del examinador. Sin embargo, con el fin de contribuir a la continuidad del trámite y atendiendo a la sugerencia del examinador, el solicitante ha decidido reemplazar dicho término con rangos específicos. En ese sentido la reivindicación 1 se modificó con el fin de hacer referencia específicamente a "*uno a siete*" átomos de flúor que se sustituyen en grupos alquilo de C₁₋₃ de R². En ese sentido amablemente se solicita al examinador reconsiderar su opinión y dar por superada la presente objeción.

- 4.3.** El examinador afirma que las reivindicaciones 6 y 7 no son claras, porque la caracterización de las respectivas formas cristalinas está incompleta. Esto debido a que aclara que cuando el patrón de difracción de rayos X se obtiene en polvo, debe complementarse con una segunda técnica cristalográfica para garantizar suficiencia. Dado que las formas reivindicadas se determinaron en polvo, es necesario adicionar otra prueba cristalográfica que complete la caracterización.

En este sentido, el solicitante manifiesta respetuosamente su desacuerdo con la opinión del examinador. Por ende, desea resaltar que un patrón de difracción de rayos X (DRX) en polvo bien definido es suficiente para cumplir con los requisitos de claridad y

reproducibilidad. La DRX es reconocida internacionalmente como una técnica de "*huella dactilar*" que identifica y distingue de forma única los polimorfos, incluso sin datos monocristalinos. Ya que un difractograma se obtienen picos característicos (2θ) de los compuestos con resultados son reproducibles entre muestras independientes bajo condiciones experimentales específicas.

Adicionalmente, el solicitante manifiesta respetuosamente que la caracterización de las formas cristalinas es completa, conforme a la evidencia presentada en la página 53, líneas 15-17, y en la página 56, líneas 30-33 de la descripción. Además del análisis por difracción de rayos X, se realizó un estudio mediante ^1H NMR, el cual, en conjunto, proporciona evidencia complementaria y concluyente tanto de la identidad molecular como de la forma cristalina del compuesto. Estos elementos permiten distinguir de manera inequívoca la forma cristalina reivindicada frente al estado de la técnica y aseguran que la invención esté suficientemente divulgada para que una persona versada en la materia pueda reproducirla.

Por lo anterior, se solicita amablemente al examinador considerar superada la presente objeción.

- 4.4.** El examinador advierte falta de claridad y concisión por tres motivos: (i) la reivindicación caracteriza el compuesto por su diana farmacológica, lo que no es adecuado; (ii) la expresión "*al menos una entidad*" sugiere múltiples principios activos sin sustento; y (iii) no se diferencia de la reivindicación 10, generando repetición de materia. Por lo tanto, el examinador sugiere modificar la redacción para que sea específica y claramente diferenciable respecto a la reivindicación de la que depende.

El solicitante manifiesta respetuosamente su desacuerdo con la opinión del examinador. Sin embargo, con el fin de contribuir a dar continuidad al proceso el solicitante ha decidido eliminar la reivindicación 11. Por ende, la objeción puede considerarse superada.

5. Consideraciones sobre la prioridad y la fecha para determinar el estado de la técnica establecida por el examinador

El examinador afirma que la reivindicación de prioridad no se acepta para las reivindicaciones 6 y 7 (renumeradas como reivindicaciones 14 y 20) porque considera que el objeto de dichas reivindicaciones no se divulga en la solicitud de prioridad, es

decir, la Solicitud de Patente JP n.º 2019206311ª ("JP '311"), presentada el 14 de noviembre de 2019 y publicada como JP2021080177A.

En ese sentido se desea resaltar que el Solicitante no reconoce el mérito de la afirmación del examinador con respecto a la reivindicación 6 (ahora reivindicación 14) ni a la reivindicación 7 (ahora reivindicación 20). Además, el solicitante manifiesta respetuosamente que, al menos la reivindicación 7 (actualmente reivindicación 20), conserva el derecho a la fecha de prioridad del 14 de noviembre de 2019, correspondiente a la fecha de presentación de la solicitud JP '311. Esto debido a que a que el Ejemplo 38 en los párrafos [0211]-[0216] del documento JP '311 (copia de su traducción al inglés adjunta para facilidad de consulta) describe las mismas condiciones experimentales descritas en el Ejemplo 38 en los párrafos [312]-[324] de la Solicitud para la síntesis de (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridina-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona cristalina. Además, el Ejemplo 38 del documento JP '311 describe los mismos datos de ¹H NMR para dicho compuesto que los proporcionados en el Ejemplo 38 de la Solicitud.

Adicionalmente, al comparar el párrafo [0216] del documento JP '311 con el párrafo [324] de la Solicitud, el documento JP '311 no divulga explícitamente la lista de picos característicos de la (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridina-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona cristalina que se mencionan en el Ejemplo 38 de la Solicitud y en la reivindicación 7 (ahora reivindicación 20). Sin embargo, una persona versada en la materia reconocería que, dado que se utiliza el mismo procedimiento de síntesis tanto en el Ejemplo 38 del documento JP '311 como en el Ejemplo 38 de la Solicitud, el producto del Ejemplo 38 del documento JP '311 es la misma (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridina-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona cristalina de la reivindicación 7 (ahora reivindicación 20) y, por lo tanto, exhibiría la mismo patrón de difracción de rayos X en polvo. Por consiguiente, la reivindicación 7 (ahora reivindicación 20) tiene fecha de prioridad del 14 de noviembre de 2019.

En ese sentido amablemente se solicita al examinador reconsiderar su opinión y para futuros exámenes considerar y reconocer la fecha de prioridad para la evaluación del capítulo reivindicatorio.

6. Nivel Inventivo

El examinador ha indicado que las reivindicaciones 1 a 4 y 10 carecerían de nivel inventivo en vista de las enseñanzas del documento D1 (WO2009004430).

Con respecto a lo anterior, me permito resaltar las disposiciones del artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina, que establecen que “*se considerará que la invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*”.

Lo anterior significa que el análisis de nivel inventivo **NO** es una comparación de los objetos de las anterioridades y la solicitud en estudio. Por el contrario, el análisis de nivel inventivo **debe demostrar** la obviedad de la invención y establecer cómo ésta no contiene un salto cualitativo, que demuestre su altura inventiva, teniendo en cuenta que se hace **necesario demostrar** que la invención analizada carece de nivel inventivo y hubiese sido obvia para una persona versada en la materia.

El análisis del examinador

El examinador señala que el documento D1 es considerado como el estado de la técnica más cercano a la invención definida en la reivindicación 1, ya que divulga compuestos derivados de feniloxazolin-2-ona como inhibidores de receptores de glutamato mGluR2 para el tratamiento de enfermedades

Por ende, el examinador considera que la diferencia entre la invención definida en la reivindicación 1 y el compuesto divulgado en D1 radica en la selección de los sustituyentes presentes en el anillo de oxazolin-2-ona. En la presente invención, R² corresponde a un alquilo C₁₋₃ opcionalmente sustituido con uno a tres átomos de flúor, mientras que R³ se define como hidrógeno o hidroxilo. Por el contrario, en los compuestos descritos en D1, la posición 4 del anillo está ocupada por un grupo metilo y la posición 5 permanece sin sustitución.

Por consiguiente, el examinador reconoce que dicha diferencia implica un efecto técnico asociado el cual corresponde a la especificidad de los compuestos de la solicitud sobre receptores NMDA en el tratamiento de enfermedades del sistema nervioso central.

De ahí que, el examinador considera que el problema técnico objetivo se formula como: ¿Cómo modificar el compuesto conocido en D1 para obtener compuestos que actúen sobre receptores NMDA?

Sin embargo, el examinador afirma que D1 ya sugiere modificaciones en el anillo de oxazolina, indicando que X_2 es O, X_3 es CR^2R^3 (donde R^2 es H y R^3 es OR con R siendo H), y en la posición 5 se encuentra $R^{11}R^{12}$ (donde R^{12} y R^{13} son alquilo) (pág. 160, reivindicación 1).

En consecuencia, una persona versada en la materia estaría motivada a seleccionar los sustituyentes e incorporar las modificaciones propuestas en D1 para llegar al objeto de la reivindicación 1, por lo cual se considera obvia. Además, el examinador considera que en el campo de la farmacología del sistema nervioso central es conocida la relación entre la potenciación de receptores de ácido glutámico (mGluR2/3) y la inhibición de receptores NMDA como estrategia terapéutica en condiciones neurológicas, como la esquizofrenia. Finalmente, las reivindicaciones dependientes 2 a 4, 10 y 11 no aportan características adicionales que confieran nivel inventivo, por lo que también se consideran carentes de dicho requisito.

La materia reclamada es inventiva a la luz del arte previo citado

El solicitante respetuosamente manifiesta su desacuerdo con la opinión del examinador. Esto debido a que la materia que reclama en el capítulo reivindicatorio de la presente invención difiere de la divulgación de D1 y presenta actividad inventiva en relación con dicho documento.

En este sentido el solicitante reconoce la autonomía de los examinadores de la oficina colombiana para emitir un concepto diferencial en la fase de examen nacional, sin embargo, desea resaltar que el nivel inventivo en relación con la materia divulgada en el documento D1 se reconoció en la fase PCT. Puntualmente, en el Informe Preliminar Internacional sobre Patentabilidad ("IPRP", el cual se adjunta una copia a este memorial para facilidad de consulta) para la Solicitud PCT n.º PCT/IB2020/000962, evaluó D1 (citado allí como D2) y determinó que las reivindicaciones PCT del solicitante se distinguen de D1. Por ejemplo, al argumentar que las reivindicaciones PCT eran novedosas, el IPRP declaró que:

"ninguno de los documentos citados D1-D4 divulga compuestos que presenten las características estructurales de los compuestos de la reivindicación 1 [PCT]".
(Véase IPRP en pág. 5, sección de Novedad)

Además, el IPRP no citó la referencia D1 en contra del nivel inventivo a ninguna de las reivindicaciones PCT.

Por otro lado, y en contraposición a lo señalado por el examinador, el solicitante sostiene respetuosamente que el documento D1 no enseña ni sugiere las modificaciones particulares que necesitaría una persona versada en la materia para modificar los compuestos del documento D1 y derivar alguna de las modalidades de compuesto reivindicadas en la presente solicitud. De hecho, el Examinador reconoce que los compuestos 61, 63, 110, 210 y 179 de D1 no contienen un grupo R² "*seleccionado entre grupos alquilo C₁₋₃*" ni un grupo R³ "*seleccionado entre grupos hidrógeno e hidroxilo*", como se indica en la reivindicación 1.

Además, incluso si los compuestos 61, 63, 110, 210 y/o 179, solos o en combinación con otras divulgaciones de D1, enseñaran o sugirieran compuestos de las presentes reivindicaciones (lo cual no ocurre), D1 no sugiere seleccionar alguno de sus compuestos, incluidos los compuestos 61, 63, 110, 210 y 179, como punto de partida para desarrollar compuestos dentro del alcance de las reivindicaciones del Solicitante. Además, al menos debido a las diferencias estructurales entre los compuestos reivindicados en esta invención y los compuestos de D1, una persona versada en la materia no habría esperado razonablemente que los compuestos de D1 tuvieran propiedades similares a las de los compuestos de esta invención. Por consiguiente, no habría utilizado D1 como punto de partida para llegar a los compuestos reivindicados en esta solicitud.

Adicionalmente, la solicitud enseña características asociadas con las modalidades de los compuestos reivindicados que no se enseñan ni sugieren en el documento D1. Por ejemplo, el *Ejemplo Experimental 1* describe un ensayo de afluencia de NR2B Ca²⁺ realizado con compuestos de la divulgación y reporta datos de actividad inhibitoria para 50 compuestos ejemplo. (Véase en detalle en la Solicitud en las páginas 65 a 67, incluida la Tabla 2).

En el Ejemplo Experimental 1 explica que, como se indica en la Tabla 2, los compuestos de la divulgación suprimieron el influjo intracelular de iones de calcio (Ca²⁺) en un receptor NMDA que contiene una subunidad NR2B, lo que confirmó que estos compuestos ejercen una acción antagonista sobre un receptor NMDA que contiene una subunidad NR2B (líneas 8-11 página 67 de la descripción).

Además, el Ejemplo Experimental 2 describe una prueba de unión *in vivo* realizada con [³H]MK-801, un compuesto capaz de unirse al sitio de apertura del receptor NMDA. (líneas 5 página 68 de la descripción Tabla 3). El Ejemplo Experimental 2 también muestra tasas de inhibición para compuestos ejemplo en la Tabla 3 y explica que los

compuestos de la divulgación inhibieron la unión de [³H]MK-801, lo que confirmó que los compuestos de esta solicitud tienen una acción antagónica funcional sobre un receptor NMDA que contiene la subunidad NR2B in vivo (líneas 12-16 página 68 de la descripción).

Teniendo en cuenta lo anteriormente expuesto, queda claro que las características técnicas de la materia definida en el capítulo reivindicatorio presentado junto al presente memorial no se derivan de manera obvia o evidente de las enseñanzas de D1. Por lo tanto, el objeto reclamado cumple con el requisito de Nivel inventivo establecido en el Art. 18 de la Decisión 486.

7. Conclusión

Con las modificaciones introducidas y los argumentos presentados puede concluirse que:

- i) El nuevo título de la solicitud es claro y se relaciona con el objeto reclamado, cumpliendo así con el literal d) del artículo 27 de la Decisión 486 de 2000;
- ii) El nuevo pliego reivindicatorio se ajusta a las disposiciones del Artículo 34 de la Decisión 486/00;
- iii) La invención de la presente solicitud es clara y cuenta con el debido sustento en el capítulo descriptivo, a la vez que se encuentra divulgada de manera suficientemente completa, cumpliendo así con los requerimientos de los Artículos 30 y 28 de la Decisión 486;
- iv) La invención de la presente solicitud no resulta obvia ni se derivada de manera evidente del estado de la técnica, cumpliendo así con los requerimientos del Artículo 18 de la Decisión 486.

Por tanto, atentamente me permito solicitar a ese Despacho otorgar el privilegio de patente solicitado a la solicitud en estudio, toda vez que cumple a cabalidad con los requerimientos de la Decisión 486 de 2000.

Asimismo, respetuosamente solicito a ese Despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional.

8. Anexos

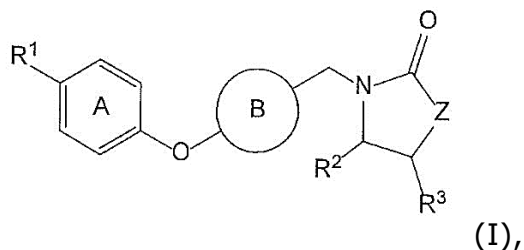
- Nuevo capítulo reivindicatorio conformado por cuarenta y tres (43) reivindicaciones.
- Anexo 1: Traducción al inglés de la Solicitud de Patente JP n.º 2019206311 tal como se presentó.
- Anexo 2: Copia del informe preliminar internacional sobre patentabilidad
- Recibo de pago por concepto de modificaciones a las reivindicaciones.
- Recibo de pago por concepto de 32 reivindicaciones.
- Recibo de pago por concepto de pago de examen de patentabilidad.

Señora Directora,


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REIVINDICACIONES

1. Un compuesto de la fórmula (I):



o una sal farmacológicamente aceptable del mismo, en donde:

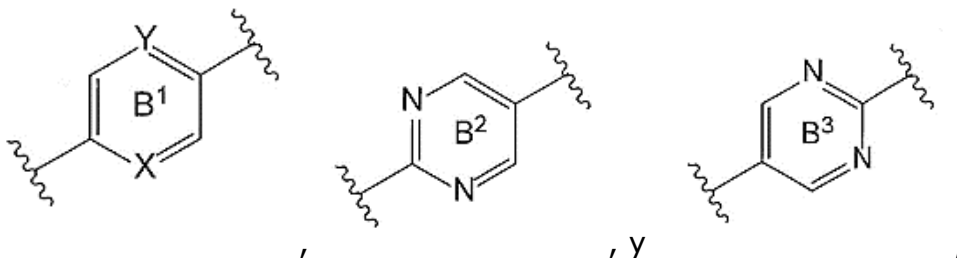
R^1 se selecciona de halógenos y grupos alquilo de C_{1-3} que no están sustituidos o están sustituidos con uno a siete átomos de flúor;

R^2 se selecciona de grupos alquilo de C_{1-3} que no están sustituidos o están sustituidos con uno a siete átomos de flúor;

R^3 se selecciona de grupos hidrógeno e hidroxil;

el anillo A se selecciona de grupos benceno que no están sustituidos o están sustituidos con uno a cuatro halógenos además R^1 y -O-anillo B;

el anillo B se selecciona de los grupos de las siguientes fórmulas:



en donde:

X y Y se seleccionan cada uno independientemente de carbono y nitrógeno;

el anillo B^1 se selecciona de grupos benceno, grupos piridina y grupos pirazina cada uno de los cuales no está sustituido o está sustituido con uno a cuatro halógenos;

el anillo B^2 se selecciona de grupos pirimidina que no están sustituidos o están sustituidos con uno a dos halógenos; y

el anillo B^3 se selecciona de grupos pirimidina que no están sustituidos o están sustituidos con uno a dos halógenos; y

Z se selecciona de CH_2 , CF_2 , O y NH.

2. El compuesto de acuerdo con la reivindicación 1 o una sal farmacológicamente aceptable del mismo, en donde:

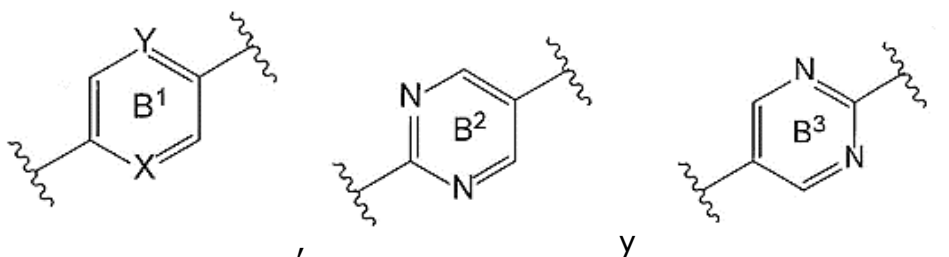
R^1 se selecciona de halógenos y grupos alquilo de C_{1-3} que no están sustituidos o están sustituidos con uno a tres átomos de flúor;

R^2 se selecciona de grupos alquilo de C_{1-3} que no están sustituidos o están sustituidos con uno a tres átomos de flúor;

R^3 se selecciona de grupos hidrógeno e hidroxilo;

el anillo A se selecciona de grupos benceno que no están sustituidos o están sustituidos con uno a cuatro halógenos;

el anillo B se selecciona de los grupos de las siguientes fórmulas:



en donde

X y Y se seleccionan cada uno independientemente de carbono y nitrógeno;

el anillo B¹ se selecciona de un grupo benceno no sustituido, grupos piridina no sustituidos y un grupo pirazina no sustituido;

el anillo B² es un grupo pirimidina no sustituido; y

el anillo B³ es un grupo pirimidina no sustituido; y

Z se selecciona de CH₂, CF₂, O y NH.

3. El compuesto de acuerdo con la reivindicación 1 o una sal farmacológicamente aceptable del mismo, en donde:

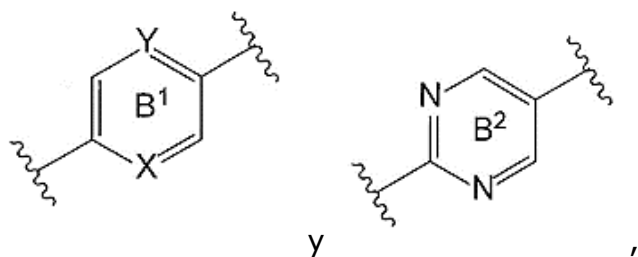
R^1 se selecciona de halógenos y grupos alquilo de C_{1-3} que no están sustituidos o están sustituidos con uno o dos átomos de flúor;

R^2 se selecciona de grupos alquilo de C_{1-3} no sustituidos;

R^3 se selecciona de grupos hidrógeno e hidroxilo;

el anillo A se selecciona de grupos benceno que no están sustituidos o están sustituidos con uno o dos halógenos;

el anillo B se selecciona de los grupos de las siguientes fórmulas:



en donde:

uno de X y Y es carbono y el otro es nitrógeno;

el anillo B¹ se selecciona de grupos piridina no sustituidos; y

el anillo B² es un grupo pirimidina no sustituido; y

Z es CH₂ u O.

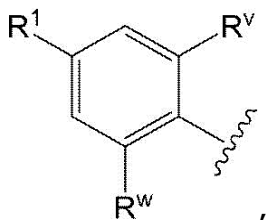
4. El compuesto de acuerdo con la reivindicación 1 o una sal farmacológicamente aceptable del mismo, en donde:

R¹ se selecciona de halógenos y grupos alquilo de C₁₋₃ que no están sustituidos o están sustituidos con uno o dos átomos de flúor;

R² se selecciona de grupos alquilo de C₁₋₃ no sustituidos;

R³ se selecciona de grupos hidrógeno e hidroxilo;

el anillo A se selecciona de los grupos de la fórmula:

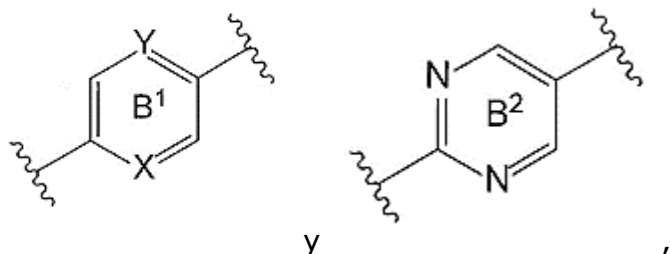


en donde:

R^v se selecciona de halógenos; y

R^w se selecciona de hidrógeno y halógenos;

el anillo B se selecciona de los grupos de las siguientes fórmulas:



en donde:

uno de X y Y es carbono y el otro es nitrógeno;

el anillo B¹ se selecciona de grupos piridina no sustituidos; y

el anillo B² es un grupo pirimidina no sustituido; y
Z es CH₂ u O.

5. El compuesto según la reivindicación 1, o una sal farmacológicamente aceptable del mismo,

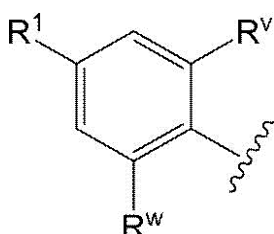
en donde:

R¹ se selecciona de halógenos y grupos alquilo de C₁₋₃ que no están sustituidos o están sustituidos con uno a tres átomos de flúor;

R² se selecciona de grupos alquilo C₁₋₃ no sustituidos;

R³ se selecciona de grupos hidrógeno e hidroxilo;

el anillo A se selecciona de grupos de la fórmula:

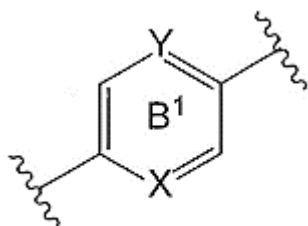


en donde:

R^V se selecciona de halógenos; y

R^W se selecciona de hidrógeno y halógenos;

el anillo B se selecciona de grupos de las siguientes fórmulas:



en donde:

X es un átomo de nitrógeno y Y es un átomo de carbono; y

el anillo B¹ no está sustituido; y

Z es CH₂.

6. El compuesto según la reivindicación 1, o una sal farmacológicamente aceptable del mismo, que es un compuesto seleccionado de entre los siguientes compuestos y sus sales farmacológicamente aceptables:

Nombre IUPAC

5-metil-1-{-[4-(4-metilfenoxi)fenil]metil}pirrolidin-2-ona

5-metil-1-{-[5-(4-metilfenoxi)pirazin-2-il]metil}pirrolidin-2-ona

5-metil-1-{-[2-(4-metilfenoxi)pirimidin-5-il]metil}pirrolidin-2-ona

(4S,5S)-4-hidroxi-5-metil-1-{-[4-(4-metilfenoxi)fenil]metil}pirrolidin-2-ona

(4S,5S)-5-etil-4-hidroxi-1-{-[4-(4-metilfenoxi)fenil]metil}pirrolidin-2-ona

5-metil-1-{-[5-(4-metilfenoxi)pirimidin-2-il]metil}pirrolidin-2-ona

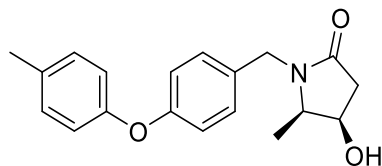
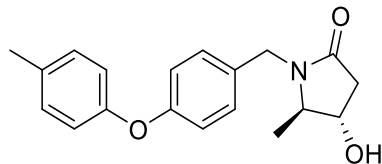
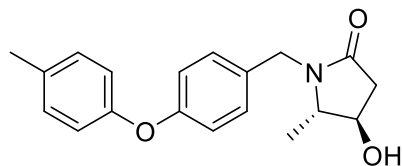
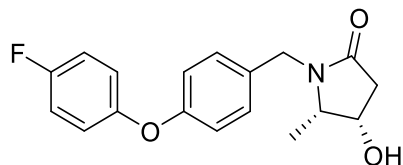
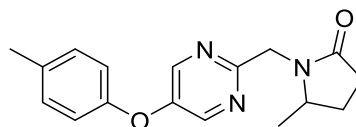
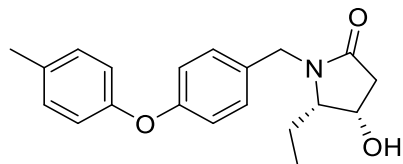
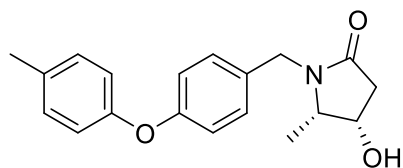
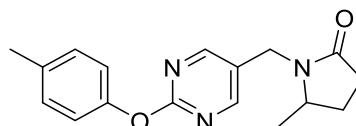
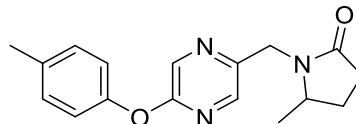
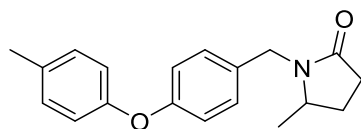
(4S,5S)-1-{-[4-(4-fluorofenoxi)fenil]metil}-4-hidroxi-5-metilpirrolidin-2-ona

(4R,5S)-4-hidroxi-5-metil-1-{-[4-(4-metilfenoxi)fenil]metil}pirrolidin-2-ona

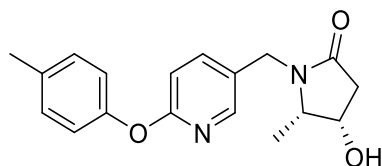
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(4R,5R)-4-hidroxi-5-metil-1-{-[4-(4-metilfenoxi)fenil]metil}pirrolidin-2-ona

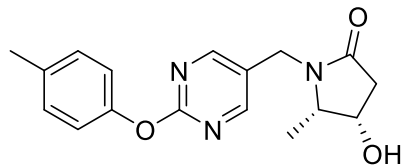
Estructura



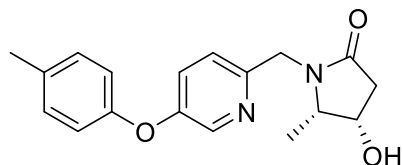
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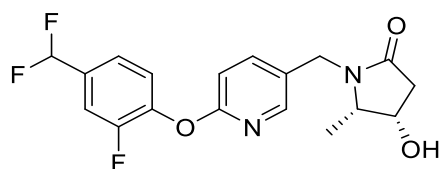
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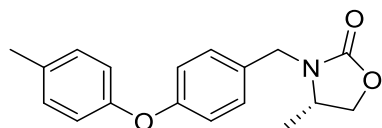
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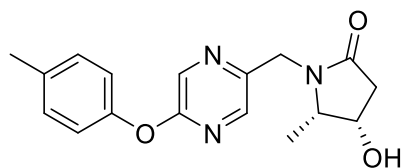
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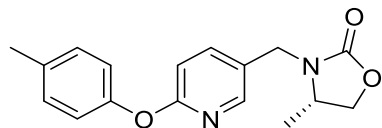
(4S)-4-metil-3-{[4-(4-metilfenoxi)fenil]metil}-1,3-oxazolidin-2-ona



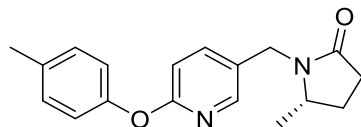
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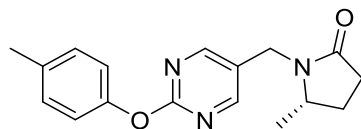
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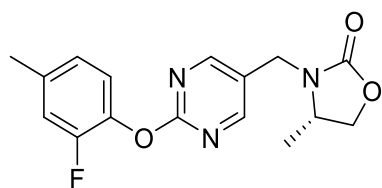
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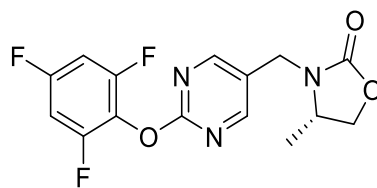
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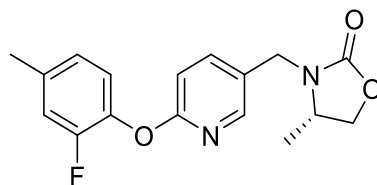
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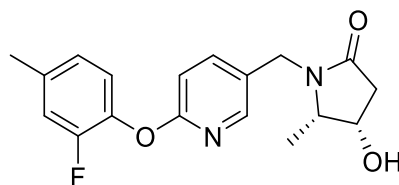
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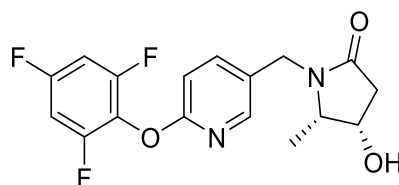
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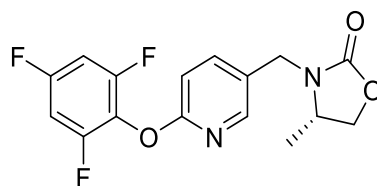
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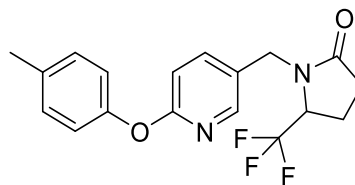
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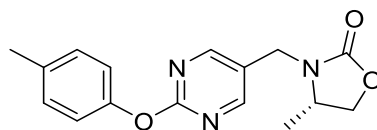
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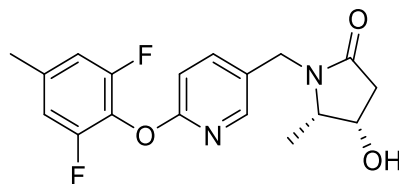
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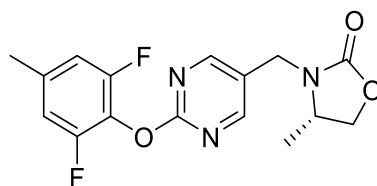
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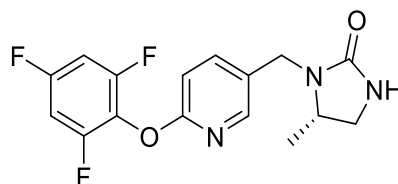
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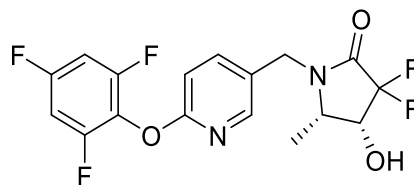
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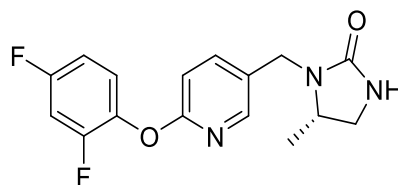
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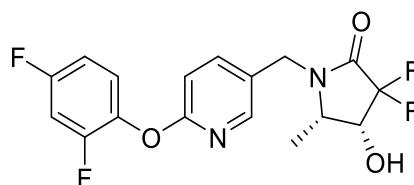
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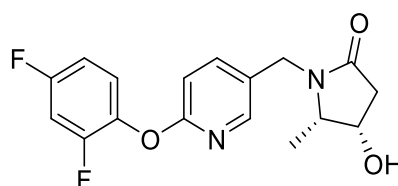
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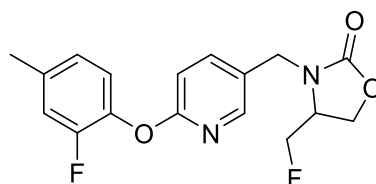
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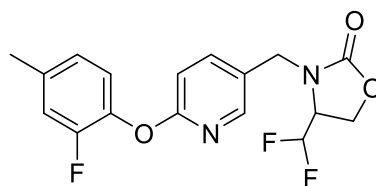
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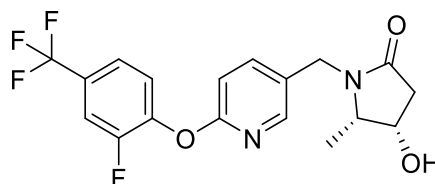
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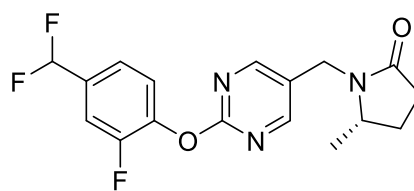
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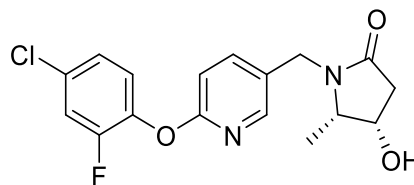
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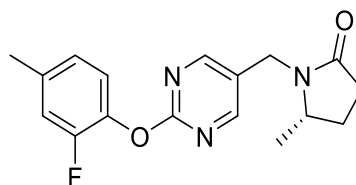
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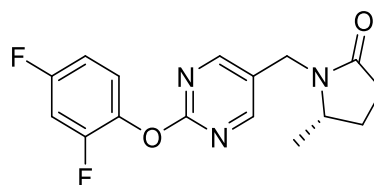
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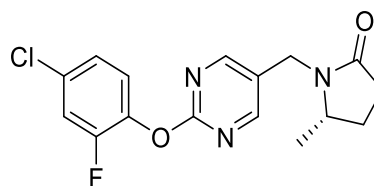
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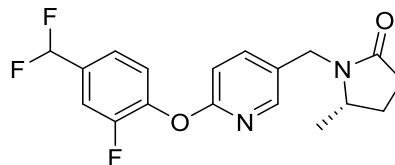
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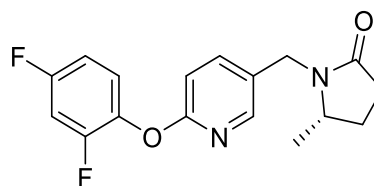
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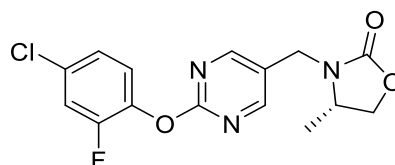
(5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-5-metilpirrolidin-2-ona



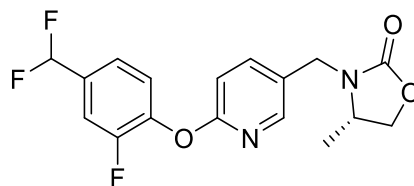
(5S)-1-{{6}-(2,4-difluorofenoxi)piridin-3-yl}metil}-5-metilpirrolidin-2-ona



(4S)-3-{{2}-(4-cloro-2-fluorofenoxi)pirimidin-5-il}metil}-4-metil-1,3-oxazolidin-2-ona



(4S)-3-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-metil-1,3-oxazolidin-2-ona



7. Un compuesto que es (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona o una sal farmacológicamente aceptable del mismo.

8. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende dos o más picos seleccionados entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

9. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende tres o más picos seleccionados entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

10. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende cuatro o más picos seleccionados entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

11. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende cinco o más picos seleccionados entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

12. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende seis o más picos seleccionados entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

13. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende siete o más picos elegidos entre los picos a $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

14. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizado por un patrón de difracción de rayos X de polvo que comprende picos 2 theta de $8,5^{\circ} \pm 0,2^{\circ}$, $11,2^{\circ} \pm 0,2^{\circ}$, $13,5^{\circ} \pm 0,2^{\circ}$, $14,6^{\circ} \pm 0,2^{\circ}$, $14,9^{\circ} \pm 0,2^{\circ}$, $19,8^{\circ} \pm 0,2^{\circ}$, $21,5^{\circ} \pm 0,2^{\circ}$ y $22,5^{\circ} \pm 0,2^{\circ}$ grados.

15. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende dos o más picos seleccionados entre los picos a $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados dos theta.

16. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende tres o más picos seleccionados entre los picos a $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados dos theta.

17. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende cuatro o más picos seleccionados entre los picos a $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados dos theta.

18. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidin-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende cinco o más picos seleccionados entre los picos a $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados dos theta.

19. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona, caracterizada por un patrón de difracción de rayos X en polvo que comprende seis o más picos elegidos entre picos a $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados dos theta.

20. Cristal (4S,5S)-1-({6-[4-(difluorometil)-2-fluorofenoxi]piridin-3-il}metil)-4-hidroxi-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X de polvo comprende picos 2 theta de $5,1^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $14,3^{\circ} \pm 0,2^{\circ}$, $16,5^{\circ} \pm 0,2^{\circ}$, $17,6^{\circ} \pm 0,2^{\circ}$, $22,3^{\circ} \pm 0,2^{\circ}$ y $25,2^{\circ} \pm 0,2^{\circ}$ grados.

21. Un compuesto que es (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona o una sal farmacológicamente aceptable del mismo.

22. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende dos o más picos seleccionados entre los picos a $7,4^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $10,5^{\circ} \pm 0,2^{\circ}$, $14,5^{\circ} \pm 0,2^{\circ}$, $16,4^{\circ} \pm 0,2^{\circ}$, $17,8^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $19,5^{\circ} \pm 0,2^{\circ}$, $20,6^{\circ} \pm 0,2^{\circ}$ y $21,3^{\circ} \pm 0,2^{\circ}$ grados dos theta.

23. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende tres o más picos seleccionados entre los picos a $7,4^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $10,5^{\circ} \pm 0,2^{\circ}$, $14,5^{\circ} \pm 0,2^{\circ}$, $16,4^{\circ} \pm 0,2^{\circ}$, $17,8^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $19,5^{\circ} \pm 0,2^{\circ}$, $20,6^{\circ} \pm 0,2^{\circ}$ y $21,3^{\circ} \pm 0,2^{\circ}$ grados dos theta.

24. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende cuatro o más picos seleccionados entre los picos a $7,4^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $10,5^{\circ} \pm 0,2^{\circ}$, $14,5^{\circ} \pm 0,2^{\circ}$, $16,4^{\circ} \pm 0,2^{\circ}$, $17,8^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $19,5^{\circ} \pm 0,2^{\circ}$, $20,6^{\circ} \pm 0,2^{\circ}$ y $21,3^{\circ} \pm 0,2^{\circ}$ grados dos theta.

25. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende cinco o más picos seleccionados entre los picos a $7,4^{\circ} \pm 0,2^{\circ}$, $10,3^{\circ} \pm 0,2^{\circ}$, $10,5^{\circ} \pm 0,2^{\circ}$, $14,5^{\circ} \pm 0,2^{\circ}$, $16,4^{\circ} \pm 0,2^{\circ}$, $17,8^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$,

19,5°±0,2°, 20,6°±0,2° y 21,3°±0,2° grados dos theta.

26. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende seis o más picos seleccionados entre los picos a 7,4° ± 0,2°, 10,3° ± 0,2°, 10,5° ± 0,2°, 14,5° ± 0,2°, 16,4° ± 0,2°, 17,8° ± 0,2°, 18,6° ± 0,2°, 19,5° ± 0,2°, 20,6° ± 0,2° y 21,3° ± 0,2° grados dos theta.

27. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende siete o más picos seleccionados entre los picos a 7,4°±0,2°, 10,3°±0,2°, 10,5°±0,2°, 14,5°±0,2°, 16,4°±0,2°, 17,8°±0,2°, 18,6°±0,2°, 19,5°±0,2°, 20,6°±0,2° y 21,3°±0,2° grados dos theta.

28. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende ocho o más picos seleccionados entre los picos a 7,4° ± 0,2°, 10,3° ± 0,2°, 10,5° ± 0,2°, 14,5° ± 0,2°, 16,4° ± 0,2°, 17,8° ± 0,2°, 18,6° ± 0,2°, 19,5° ± 0,2°, 20,6° ± 0,2° y 21,3° ± 0,2° grados dos theta.

29. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende nueve o más picos seleccionados entre los picos a 7,4° ± 0,2°, 10,3° ± 0,2°, 10,5° ± 0,2°, 14,5° ± 0,2°, 16,4° ± 0,2°, 17,8° ± 0,2°, 18,6° ± 0,2°, 19,5° ± 0,2°, 20,6° ± 0,2° y 21,3° ± 0,2° grados dos theta.

30. Cristal (5S)-1-{[2-(2,4-difluorofenoxi)pirimidin-5-il]metil}-5-metilpirrolidina-2-ona caracterizado por un patrón de difracción de rayos X en polvo que comprende picos a 7,4°±0,2°, 10,3°±0,2°, 10,5°±0,2°, 14,5°±0,2°, 16,4°±0,2°, 17,8°±0,2°, 18,6°±0,2°, 19,5°±0,2°, 20,6°±0,2° y 21,3°±0,2° grados dos theta.

31. Un compuesto que es (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona o una sal farmacológicamente aceptable del mismo.

32. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-

oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende dos o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

33. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende tres o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

34. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende cuatro o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

35. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende cinco o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

36. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende seis o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

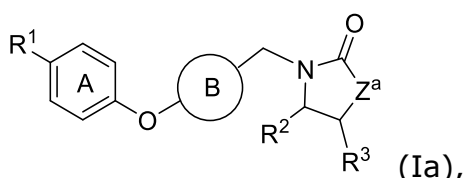
37. Cristal (4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende siete o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

38. Cristal(4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona, caracterizado por un patrón de difracción de rayos X en polvo que comprende ocho o más picos seleccionados entre los picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

39. Cristal(4S)-3-{[2-(4-cloro-2-fluorofenoxi)pirimidin-5-il]metil}-4-metil-1,3-oxazolidina-2-ona caracterizado por un patrón de difracción de rayos X en polvo que comprende picos a $5,4^{\circ} \pm 0,2^{\circ}$, $14,0^{\circ} \pm 0,2^{\circ}$, $16,3^{\circ} \pm 0,2^{\circ}$, $17,4^{\circ} \pm 0,2^{\circ}$, $18,6^{\circ} \pm 0,2^{\circ}$, $20,3^{\circ} \pm 0,2^{\circ}$, $21,0^{\circ} \pm 0,2^{\circ}$, $21,8^{\circ} \pm 0,2^{\circ}$ y $24,5^{\circ} \pm 0,2^{\circ}$ grados dos theta.

40. Una composición farmacéutica que comprende una entidad seleccionada de los compuestos de acuerdo con cualquier una de las reivindicaciones 1-7, 21 y 31 y sales farmacológicamente aceptables de los mismos, y formas cristalinas según cualquiera de las reivindicaciones 8 a 20, 22 a 30 y 32 a 39; y un vehículo farmacológicamente aceptable.

41. Un proceso para preparar un compuesto de Fórmula (Ia), o una sal farmacológicamente aceptable del mismo,

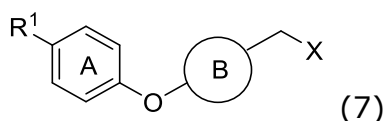


en donde

Z^a es CH_2 , CF_2 u O; y

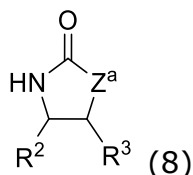
R^1 , R^2 , R^3 , el anillo A y el anillo B son como se definen en la reivindicación 1, que comprende:

someter el compuesto (7)



donde X se elige entre halógenos,

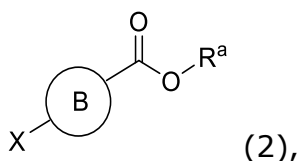
a una reacción de alquilación junto con el compuesto (8)



para obtener el compuesto de Fórmula (Ia).

42. El proceso de la reivindicación 41, donde el compuesto (7) se prepara mediante

(i) someter el compuesto (2)

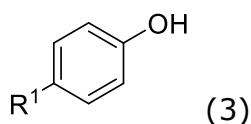


en donde

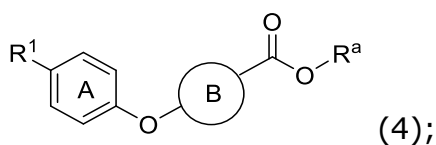
X es halógeno; y

R^a es alquilo C₁₋₃ que no está sustituido o está sustituido con uno a tres sustituyentes seleccionados de halógenos,

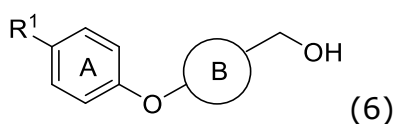
a una reacción de sustitución nucleofílica aromática junto con el compuesto (3)



para obtener el compuesto (4)

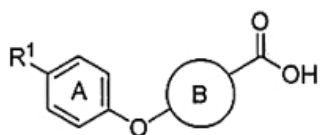


(iia) someter el compuesto (4) a una reacción de reducción para obtener el compuesto (6);



o

(iib) hidrolizar el compuesto (4) para obtener el compuesto (5)



(5), y

someter el compuesto (5) a una reacción de reducción para obtener el compuesto

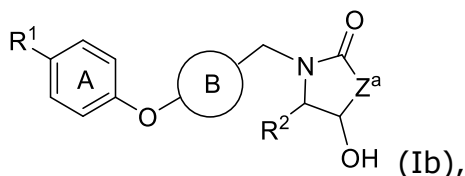
(6);

y

(iii) halogenar un grupo hidroxilo del compuesto (6)

para obtener el compuesto (7).

43. Un proceso para preparar un compuesto de Fórmula (Ib), o una sal farmacológicamente aceptable del mismo,

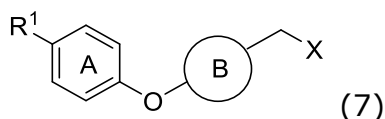


en donde

Z^a es CH₂, CF₂ o O; y

R¹, R², el anillo A y el anillo B son como se definen en la reivindicación 1, que comprende:

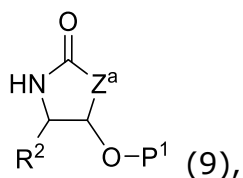
(i) someter el compuesto (7)



(7)

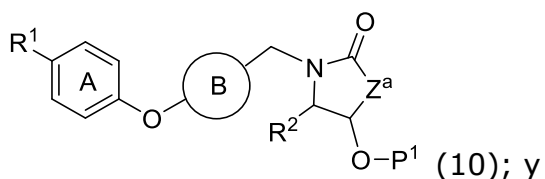
donde X se elige entre halógenos,

a una reacción de alquilación junto con el compuesto (9)



(9),

donde P¹ es un grupo protector de hidroxilo alcohólico, para obtener el compuesto (10)



(10); y

(ii) desproteger el compuesto (10)
para obtener el compuesto de fórmula (Ib).

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[Document Name] Specification 1
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HETEROCYCLIC COMPOUND AND USE THEREOF

[Technical Field]

[0001]

The present invention relates to a heterocyclic compound that can have an antagonistic effect of an N-methyl-D-aspartic acid (NMDA) receptor containing the NR2B subunit and is anticipated to be useful as a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, peripheral symptoms of dementia, or the like.

[0002]

(Background Art)

The major excitatory neurotransmitter in the central nervous system such as the brain and spinal cord is glutamate, and the signal transduction thereof is carried out by the ion channel-conjugated receptor N-methyl-D-aspartic acid (NMDA) receptor, the gamma-amino-3-hydroxy-5-methylxazole-4-propionic acid (AMPA) / kainic acid (KA) receptor, and the metabotropic glutamate receptor. Among these, the NMDA receptor has high permeability to the cation including calcium ions, and mediates excitatory neurotransmission by depolarization of the nerve cells. In addition, calcium that has flowed into the cell via the NMDA receptor functions as a secondary messenger and causes plastic nerve function changes via effects such as changes in intracellular phosphorylation signals and regulation of gene transcription and translation, and thus the NMDA receptors play an important role in the regulation of central nervous system function.

The NMDA receptor is a receptor composed of a tetramer in which two or three subunits of NR1, NR2A, NR2B, NR2C, NR2D, NR3A, or NR3B subunits are associated, and the presence of the NR1 subunit is essential to have a function as a receptor for carrying out the excitatory neurotransmission. Since the NR1 subunit is included in all the NMDA receptors having functions, it is widely distributed in the central nervous system. On the other hand, the distribution and expression timing of the NR2 subunit are different for each subunit. For example, the NR2A and NR2C subunits are detected for the first time immediately before birth, while the NR2B and NR2D subunits are observed from the early stage of fetal development. Moreover, for example, the NR2A subunit is widely distributed in the brain, while the NR2B subunit is locally expressed in the forebrain, and the NR2C subunit is locally expressed in the cerebellum (non-patent literature 1).

The NMDA receptor containing the NR2B subunit as the target in the present invention is highly expressed in the cerebral cortex (particularly layers 2 and 3), hippocampus, amygdala, ventral nucleus of thalamus, and olfactory bulb in the adult rodent brain. Also, in the spinal cord, the receptor is localized to the posterior horn of the spinal cord (particularly the second layer) (non-patent literature 2). In addition, in the single cell, the NMDA receptor containing the NR2B subunit is most expressed in postsynaptic density and expression thereof is also observed in the

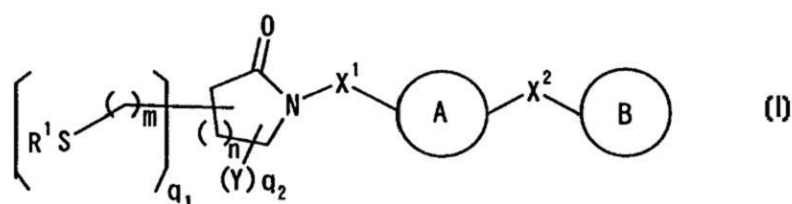
extrasynaptic region (non-patent literature 3). This suggests that the NMDA receptor containing the NR2B subunit is widely functional in the brain and effective in the prevention and treatment of central nervous system diseases.

[0003]

- 5 In patent literature 1, a following compound having a matrix metalloprotease inhibitory effect and useful for prevention and treatment of osteoarthritis, cancer, autoimmune disease, and the like, is disclosed.

[0004]

[Chemical Formula 1]



10

[0005]

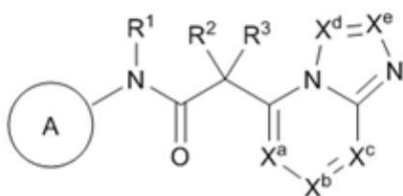
[In the formula, each symbol is as defined in the document.]

In patent literature 2, a following compound having a NMDA NR2B subunit-specific negative allosteric modulatory effect and useful for prevention and treatment of major depression, bipolar disorder, migraine, pain, peripheral symptoms of dementia, or the like, is disclosed.

15

[0006]

[Chemical Formula 2]



[0007]

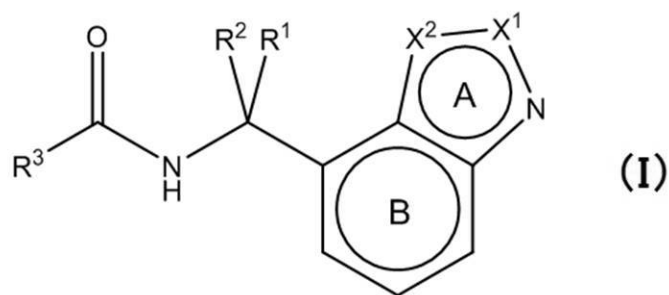
- 20 [In the formula, each symbol is as defined in the document.]

In patent literature 3, a following compound having an antagonistic action of an N-methyl-D-aspartic acid (NMDA) receptor containing the NR2B subunit, and useful as a prevention and treatment of major depression, bipolar disorder, migraine, pain, peripheral symptoms of dementia, or the like, is disclosed.

25

[0008]

[Chemical Formula 3]



[0009]

[In the formula, each symbol is as defined in the document.]

[Prior Art Literature]

5 [Patent Literature]

[0010]

[Patent Literature 1] WO 00/17162

[Patent Literature 2] WO 2016/104434

[Patent Literature 3] WO 2019/022179

10 [Non-Patent Literature]

[0011]

[Non-Patent Literature 1] Neuron (Neuron), Vol. 12, page 529 to 540, 1994

[Non-Patent Literature 2] The Journal of Comparative Neurology (J. Comp. Neurol.) Vol. 338, page 377 to 390, 1993

15 [Non-Patent Literature 3] Molecules and Cells (Mol. Cells), Vol. 7, page 64 to 71, 1997

[Summary of Invention]

[Problem to be Solved by Invention]

[0012]

20 An objective of the present invention is to provide a heterocyclic compound, and a pharmaceutical containing such, that can have an antagonistic effect of the NMDA receptor containing the NR2B subunit and is anticipated to be useful as a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, peripheral symptoms of dementia, or the like.

[Means for Solving Problem]

[0013]

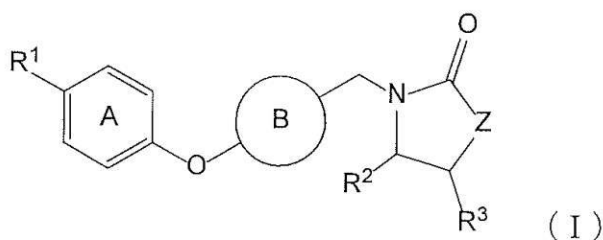
25 As a result of the intensive study to solve the problem, the present inventors have found that the compound shown by formula (I) below can have antagonistic effect of the NMDA receptor containing an excellent NR2B subunit and completed the present invention.

That is, the present invention is as follows.

[1] A compound or a salt thereof represented by formula (I):

30 [0014]

[Chemical Formula 4]



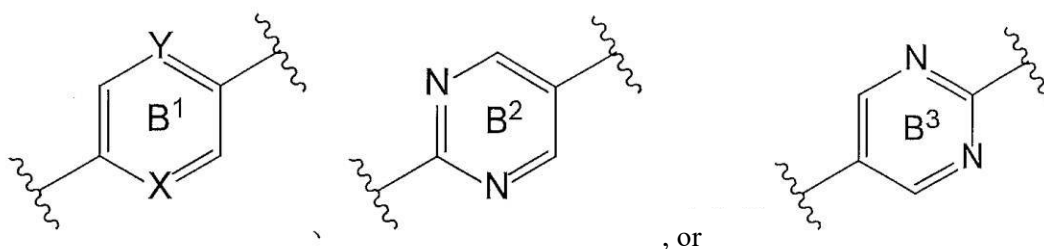
[0015]

[In the formula,

- 5 R^1 indicates a C_{1-3} alkyl group or a halogen atom that may be substituted with a fluorine atom;
 R^2 indicates a C_{1-3} alkyl group that may be substituted with a fluorine atom;
 R^3 indicates a hydrogen atom or a hydroxy group;
 ring A indicates a benzene ring that may be further substituted;
 ring B indicates

10 [0016]

[Chemical Formula 5]



[0017]

(in the formula,

- 15 X and Y each independently represent a carbon atom or a nitrogen atom;
 ring B^1 indicates a benzene ring, a pyridine ring, or a pyrazine ring that each may be further substituted; and
 ring B^2 and ring B^3 each indicate a pyrimidine ring that may be further substituted)
 ; and
20 Z indicates CH_2 , CF_2 , O, or NH .]

(in the present specification, it may be abbreviated as "compound (I)").

[2] A pharmaceutical containing the compound according to [1] or a salt thereof.

[3] The pharmaceutical according to [2], wherein the pharmaceutical is an antagonist of an NMDA receptor containing a NR2B subunit.

- 25 [4] The pharmaceutical according to [2], wherein the pharmaceutical is a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, or peripheral symptoms of dementia.

[Effect of Invention]

[0018]

The present invention provides a heterocyclic compound, and a pharmaceutical containing such, that can have an antagonistic effect of the NMDA receptor containing the NR2B subunit and is anticipated to be useful as a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, peripheral symptoms of dementia, or the like.

[0019]

(Detailed Description of Invention)

The definition of each substituent used in the present specification is described in detail below.

Each substituent has the following definitions unless otherwise specified.

Examples of the "halogen atom" include fluorine, chlorine, bromine, and iodine in the present specification.

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

In the present specification, examples of the "C₁₋₆ alkyl group that may be halogenated" include a C₁₋₆ alkyl group that may have one to seven halogen atoms, preferably one to five halogen atoms.

Specific examples include a methyl group, a chloromethyl group, a difluoromethyl group, a trichloromethyl group, a trifluoromethyl group, an ethyl group, a 2-bromoethyl group, a 2,2,2-trifluoroethyl group, a tetrafluoroethyl group, a pentafluoroethyl group, a propyl group, a 2,2-difluoropropyl group, a 3,3,3-trifluoropropyl group, an isopropyl group, a butyl group, a 4,4,4-trifluorobutyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a 5,5,5-trifluoropentyl group, a hexyl group, and a 6,6,6-trifluorohexyl group.

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

In the present specification, examples of the "C₂₋₆ alkynyl group" include an ethynyl group, a 1-propynyl group, a 2-propynyl group, a 1-butylnyl group, a 2-butylnyl group, a 3-butylnyl group, a 1-pentylnyl group, a 2-pentylnyl group, a 3-pentylnyl group, a 4-pentylnyl group, a 1-hexynyl group, a

2-hexynyl group, a 3-hexynyl group, a 4-hexynyl group, a 5-hexynyl group, and a 4-methyl-2-pentynyl group.

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

10 In the present specification, examples of the "C₃₋₁₀ cycloalkyl group that may be halogenated" include a C₃₋₁₀ cycloalkyl group that may have one to seven halogen atoms, preferably one to five halogen atoms. Specific examples include a cyclopropyl group, a 2,2-difluorocyclopropyl group, a 2,3-difluorocyclopropyl group, a cyclobutyl group, a difluorocyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, and a cyclooctyl group.

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

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

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

[0020]

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

25 In the present specification, examples of the "C₁₋₆ alkoxy group that may be halogenated" include a C₁₋₆ alkoxy group that may have one to seven halogen atoms, preferably one to five halogen atoms. Specific examples include a methoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2,2,2-trifluoroethoxy group, a propoxy group, an isopropoxy group, a butoxy group, a 4,4,4-trifluorobutoxy group, an isobutoxy group, a sec-butoxy group, a pentyloxy group, and a hexyloxy group.

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

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

In the present specification, examples of the "C₁₋₆ alkylthio group that may be halogenated" include a C₁₋₆ alkylthio group that may have one to seven halogen atoms, preferably one to five halogen atoms. Specific examples include a methylthio group, a difluoromethylthio group, a trifluoromethylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, a 4,4,4-trifluorobutylthio group, a pentylthio group, and a hexylthio group.

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

In the present specification, examples of the "C₁₋₆ alkyl-carbonyl group that may be halogenated" include a C₁₋₆ alkyl-carbonyl group that may have one to seven halogen atoms, preferably one to five halogen atoms. Specific examples include an acetyl group, a chloroacetyl group, a trifluoroacetyl group, a trichloroacetyl group, a propanoyl group, a butanoyl group, a pentanoyl group, and a hexanoyl group.

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

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

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

In the present specification, examples of the "5- to 14-membered aromatic heterocyclic carbonyl group" include a nicotinoyl group, an isonicotinoyl group, a tenoyl group, and a furoyl group.

In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclic carbonyl group" include a morpholinyl carbonyl group, a piperidinyl carbonyl group, and a pyrrolidinyl carbonyl group.

[0021]

In the present specification, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl group" included a methyl carbamoyl group, an ethyl carbamoyl group, a dimethyl carbamoyl group, a diethyl carbamoyl group, and an N-ethyl-N-methyl carbamoyl group.

In the present specification, examples of the "mono- or di-C₇₋₁₆ aralkyl-carbamoyl group" include a benzyl carbamoyl group and a phenethyl carbamoyl group.

In the present specification, examples of the "C₁₋₆ alkylsulfonyl group" include a methylsulfonyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, a sec-butylsulfonyl group, and a tert-butylsulfonyl group. In the present specification, examples of the "C₁₋₆ alkylsulfonyl group that may be halogenated" include a C₁₋₆ alkylsulfonyl group that may have one to seven halogen atoms, preferably one to five halogen atoms. Specific examples include a methylsulfonyl group, a difluoromethylsulfonyl group, a trifluoromethylsulfonyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, a 4,4,4-trifluorobutylsulfonyl group, a pentylsulfonyl group, and a hexylsulfonyl group.

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

[0022]

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

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

[0023]

In the present specification, examples of the "hydrocarbon group that may be substituted" include a hydrocarbon group that may have a substituent selected from the following substituent group A.

[Substituent Group A]

(1) A halogen atom,

(2) a nitro group,

(3) a cyano group,

(4) an oxo group,

(5) a hydroxy group,

(6) a C₁₋₆ alkoxy group that may be halogenated,

(7) a C₆₋₁₄ aryloxy group (for example, a phenoxy group and a naphthoxy group),

(8) a C₇₋₁₆ aralkyloxy group (for example, a benzyloxy group),

(9) a 5- to 14-membered aromatic heterocyclic oxy group (for example, a pyridyloxy group),

- (10) a 3- to 14-membered non-aromatic heterocyclic oxy group (for example, a morpholinyl group and a piperidinyl group),
- (11) a C₁₋₆ alkyl-carbonyloxy group (for example, an acetoxy group and a propanoyloxy group),
- (12) a C₆₋₁₄ aryl-carbonyloxy group (for example, a benzoyloxy group, a 1-naphthoyloxy group, and a 2-naphthoyloxy group),
- (13) a C₁₋₆ alkoxy-carbonyloxy group (for example, a methoxycarbonyloxy group, an ethoxycarbonyloxy group, a propoxycarbonyloxy group, and a butoxycarbonyloxy group), (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (for example, a methylcarbamoyloxy group, an ethylcarbamoyloxy group, a dimethylcarbamoyloxy group, and a diethylcarbamoyloxy group),
- (15) a C₆₋₁₄ aryl-carbamoyloxy group (for example, a phenylcarbamoyloxy group and a naphthylcarbamoyloxy group),
- (16) a 5- to 14-membered aromatic heterocyclic carbonyloxy group (for example, a nicotinoyloxy group), (17) a 3- to 14-membered non-aromatic heterocyclic carbonyloxy group (for example, a morpholinylcarbonyloxy group and a piperidinylcarbonyloxy group),
- (18) a C₁₋₆ alkylsulfonyloxy group that may be halogenated (for example, a methylsulfonyloxy group and a trifluoromethylsulfonyloxy group), (19) a C₆₋₁₄ arylsulfonyloxy group that may be substituted with a C₁₋₆ alkyl group (for example, a phenylsulfonyloxy group and a toluenesulfonyloxy group),
- (20) a C₁₋₆ alkylthio group that may be halogenated,
- (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,
- (23) a formyl group,
- (24) a carboxy group,
- (25) a C₁₋₆ alkyl-carbonyl group that may be halogenated,
- (26) a C₆₋₁₄ aryl-carbonyl group,
- (27) a 5- to 14-membered aromatic heterocyclic carbonyl group,
- (28) a 3- to 14-membered non-aromatic heterocyclic carbonyl group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- (30) a C₆₋₁₄ aryloxy-carbonyl group (for example, phenyloxycarbonyl group, a 1-naphthyloxycarbonyl group, and a 2-naphthyloxycarbonyl group),
- (31) a C₇₋₁₆ aralkyloxy-carbonyl group (for example, a benzyloxycarbonyl group and a phenethyloxycarbonyl group),
- (32) a carbamoyl group,
- (33) a thiocarbamoyl group,
- (34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,

- (35) a C₆₋₁₄ aryl-carbamoyl group (for example, a phenylcarbamoyl group),
- (36) a 5- to 14-membered aromatic heterocyclic carbamoyl group (for example, a pyridylcarbamoyl group and a thienylcarbamoyl group),
- (37) a 3- to 14-membered non-aromatic heterocyclic carbamoyl group (for example, a morpholinylcarbamoyl group and a piperidinylcarbamoyl group),
- (38) a C₁₋₆ alkylsulfonyl group that may be halogenated,
- (39) a C₆₋₁₄ arylsulfonyl group,
- (40) a 5- to 14-membered aromatic heterocyclic sulfonyl group (for example, a pyridylsulfonyl group and a thienylsulfonyl group),
- (41) a C₁₋₆ alkylsulfonyl group that may be halogenated,
- (42) a C₆₋₁₄ arylsulfinyl group (for example, a phenylsulfinyl group, a 1-naphthylsulfinyl group, and a 2-naphthylsulfinyl group),
- (43) a 5- to 14-membered aromatic heterocyclic sulfinyl group (for example, a pyridylsulfinyl group and a thienylsulfinyl group),
- (44) an amino group,
- (45) a mono- or di-C₁₋₆ alkylamino group (for example, a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a butylamino group, a dimethylamino group, a diethylamino group, a dipropylamino group, a dibutylamino group, and an N-ethyl-N-methylamino group),
- (46) a mono- or di-C₆₋₁₄ arylamino group (for example, a phenylamino group),
- (47) a 5- to 14-membered aromatic heterocyclic amino group (for example, a pyridylamino group),
- (48) a C₇₋₁₆ aralkylamino group (for example, a benzylamino group),
- (49) a formylamino group,
- (50) a C₁₋₆ alkyl-carbonylamino group (for example, an acetylamino group, a propanoylamino group, and a butanoylamino group),
- (51) a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (for example, an N-acetyl-N-methylamino group),
- (52) a C₆₋₁₄ aryl-carbonylamino group (for example, a phenylcarbonylamino group and a naphthylcarbonylamino group),
- (53) a C₁₋₆ alkoxy-carbonylamino group (for example, a methoxycarbonylamino group, an ethoxycarbonylamino group, a propoxycarbonylamino group, a butoxycarbonylamino group, and a tert-butoxycarbonylamino group),

- (54) a C₇₋₁₆ aralkyloxy-carbonylamino group (for example, a benzyloxycarbonylamino group),
(55) a C₁₋₆ alkylsulfonylamino group (for example, a methylsulfonylamino group and an ethylsulfonylamino group),
(56) a C₆₋₁₄ arylsulfonylamino group that may be substituted with a C₁₋₆ alkyl group (for example,
5 a phenylsulfonylamino group and a toluenesulfonylamino group),
(57) a C₁₋₆ alkyl group that may be halogenated,
(58) a C₂₋₆ alkenyl group,
(59) a C₂₋₆ alkynyl group,
(60) a C₃₋₁₀ cycloalkyl group,
10 (61) a C₃₋₁₀ cycloalkenyl group, and
(62) a C₆₋₁₄ aryl group.

[0024]

The number of the substituents in the "hydrocarbon group that may be substituted" is, for example, one to five, preferably one to three. When the number of substituents is two or more,
15 each substituent may be the same or may be different.

In the present specification, examples of the "heterocyclic group" (including the "heterocyclic group" in the "heterocyclic group that may be substituted") include (i) an aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group, and (iii) a 7- to 10-membered bridged-ring heterocyclic group each containing 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom,
20 and an oxygen atom in addition to a carbon atom as ring constituent atoms.

[0025]

In the present specification, examples of the "aromatic heterocyclic group" (including the "5- to 14-membered aromatic heterocyclic group") include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom, and an oxygen atom in addition to a carbon atom as ring constituent atoms.
25

Suitable examples of the "aromatic heterocyclic group" include a 5- to 6-membered monocyclic aromatic heterocyclic group such as a thienyl group, a furyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, an isothiazolyl group, an oxazolyl group, an isoxazolyl group, a pyridyl group, a pyrazinyl group, a pyrimidinyl group, a pyridadinyl group, a 1,2,4-oxadiazolyl group, a 1,3,4-oxadiazolyl group, a 1,2,4-thiadiazolyl group, a 1,3,4-thiadiazolyl, a triazolyl group, a tetrazolyl group, and a triazinyl group; and
30 a 8- to 14-membered condensed polycyclic (preferably bi- or tricyclic) aromatic heterocyclic group such as a benzothiophenyl group, a benzofuranyl group, a benzimidazolyl group, a benzoxazolyl group, a benzisoxazolyl group, a benzothiazolyl group, a benzoisothiazolyl group, a benzotriazolyl group, an imidazopyridinyl group, a thienopyridinyl group, a furopyridinyl group, a
35

pyrrolopyridinyl group, a pyrazolopyridinyl group, an oxazolopyridinyl group, a thiazolopyridinyl group, an imidazopyradinyl group, an imidazopyridinyl group, a thienopyrimidinyl group, a furopyrimidinyl group, a pyrrolopyrimidinyl group, a pyrazolopyrimidinyl group, an oxazolopyrimidinyl group, a thiazolopyrimidinyl group, a pyrazolotriadinyl group, a naft [2,3-b] thienyl group, a phenoxathiinyl group, an indolyl group, an isoindolyl group, a 1H-indazolyl group, a purinyl group, an isoquinolyl group, a quinolyl group, a phthalazinyl group, a naphthyridinyl group, a quinoxalinyl group, a quinazolinyl group, a cinnolyl group, a carbazolyl group, a β -carbolinyl group, a phenanthridinyl group, an acridinyl group, a phenazinyl group, a phenothiazinyl group, and a phenoxadiny group.

[0026]

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

Suitable examples of the "non-aromatic heterocyclic group" include 3- to 8-membered monocyclic non-aromatic heterocyclic groups such as an aziridinyl group, an oxylanyl group, a thiiranyl group, an azetidiny group, an oxetanyl group, a thietanyl group, a tetrahydrothienyl group, a tetrahydrofuranyl group, a pyrrolinyl group, a pyrrolidinyl group, an imidazolinyl group, an imidazolidinyl group, an oxazolinyl group, an oxazolydiny group, a pyrazolinyl group, a pyrazolydiny group, a thiazolinyl group, a thiazolidinyl group, a tetrahydroisothiazolyl group, a tetrahydrooxazolyl group, a tetrahydroisooxazolyl group, a piperidinyl group, a piperazinyl group, a tetrahydropyridinyl group, a dihydropyridinyl group, a dihydrothiopyranyl group, a tetrahydropyrimidinyl group, a tetrahydropyridazinyl group, a dihydropyranyl group, a tetrahydropyranyl group, a tetrahydrothiopyranyl group, a morpholinyl group, a thiomorpholinyl group, an azepanyl group, a diazepanyl group, an azepinyl group, an oxepanyl group, an azocanyl group, and a diazocanyl group; and

a 9- to 14-membered condensed polycyclic (preferably bi- or tricyclic) non-aromatic heterocyclic group such as a dihydrobenzofuranyl group, a dihydrobenzoimidazolyl group, a dihydrobenzoxazolyl group, a dihydrobenzothiazolyl group, a dihydrobenzoisothiazolyl group, a dihydronaphtho [2,3-b] thienyl group, a tetrahydroisoquinolyl group, a tetrahydroquinolyl group, a 4H-quinolidinyl group, an indolinyl group, an isoindolinyl group, a tetrahydrothieno [2,3-c] pyridinyl group, a tetrahydrobenzoazepinyl group, a tetrahydroquinoxalinyl group, a tetrahydrophenanthridinyl group, a hexahydrophenothiazinyl group, a hexahydrophenoxadiny group, a tetrahydrophthalazinyl group, a tetrahydronaphthiridinyl group, a tetrahydroquinazolinyl

group, a tetrahydrocinnoliny group, a tetrahydrocarbazolyl group, a tetrahydro- β -carboliny group, a tetrahydroacridiny group, a tetrahydrophenaziny group, a tetrahydrothioxanthenyl group, and an octahydroisoquinolyl group.

[0027]

5 In the present specification, suitable examples of the "7- to 10-membered bridged-ring heterocyclic group" include a quinuclidiny group and a 7-azabicyclo [2.2.1] heptany group.

In the present specification, suitable examples of the "nitrogen-containing heterocyclic group" include, among the "heterocyclic groups," the one containing at least one or more nitrogen atoms as ring-constituting atoms.

10 In the present specification, examples of the "heterocyclic group that may be substituted" include a heterocyclic group that may have a substituent selected from the following substituent group A.

The number of substituents in the "heterocyclic group which may be substituted" is, for example, one to three. When the number of substituents is two or more, each substituent may be the same or may be different.

15 [0028]

In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfiny group, a sulfo group, a sulfamoyl group, and a phosphono group that each may have the "one or two substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a 5- to 14-membered aromatic heterocyclic group, and a 3- to 14-membered non-aromatic heterocyclic group that each may have one to three substituents selected from a halogen atom and a C₁₋₆ alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group, and a carbamoyl group that may be halogenated."

25 In addition, examples of the "acyl group" include a hydrocarbon-sulfonyl group, a heterocyclic-sulfonyl group, a hydrocarbon-sulfinyl group, and a heterocyclic-sulfinyl group.

Here, respectively, the hydrocarbon-sulfonyl group means a sulfonyl group to which a hydrocarbon group is bound, the heterocyclic-sulfonyl group means a sulfonyl group to which a heterocyclic group is bound, the hydrocarbon-sulfinyl group means a sulfinyl group to which a hydrocarbon group is bound, and the heterocyclic-sulfinyl group means a sulfinyl group to which a heterocyclic group is bound.

Suitable examples of the "acyl group" include a formyl group, a carboxy group, a C₁₋₆ alkyl-carbonyl group, a C₂₋₆ alkenyl-carbonyl group (for example, a crotonoyl group), a C₃₋₁₀ cycloalkyl-carbonyl group (for example, a cyclobutanecarbonyl group, a cyclopentanecarbonyl group, a cyclohexanecarbonyl group, and a cycloheptanecarbonyl group), a C₃₋₁₀ cycloalkenyl-carbonyl group (for example, a 2-cyclohexenecarbonyl group), a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-

carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (for example, a phenyloxycarbonyl group and a naphthyloxycarbonyl group), a C₇₋₁₆ aralkyloxy-carbonyl group (for example, a benzyloxycarbonyl group and a phenethyloxycarbonyl group), a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (for example, a diallyl carbamoyl group), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (for example, a cyclopropylcarbamoyl group), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (for example, a phenylcarbamoyl group), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclic carbamoyl group (for example, a pyridylcarbamoyl group), a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (for example, a methylthiocarbamoyl group and an N-ethyl-N-methylthiocarbamoyl group), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (for example, a diallylthiocarbamoyl group), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (for example, a cyclopropylthiocarbamoyl group and a cyclohexylthiocarbamoyl group), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (for example, a phenylthiocarbamoyl group), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (for example, a benzylthiocarbamoyl group and a phenethylthiocarbamoyl group), a 5- to 14-membered aromatic heterocyclic thiocarbamoyl group (for example, a pyridylthiocarbamoyl group), a sulfinio group, a C₁₋₆ alkylsulfinyl group (for example, a methylsulfinyl group and an ethylsulfinyl group), a sulfo group, a C₁₋₆ alkylsulfonyl group, a C₆₋₁₄ arylsulfonyl group, a phosphono group, and a mono- or di-C₁₋₆ alkylphosphono group (for example, a dimethylphosphono group, a diethylphosphono group, a diisopropylphosphono group, and a dibutylphosphono group).

[0029]

In the present specification, examples of the “amino group that may be substituted” include an amino group that may have “one or two substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group, and a C₆₋₁₄ arylsulfonyl group that each may have one to three substituents selected from the substituent group A.”

Suitable examples of the amino group that may be substituted include an amino group, a mono- or di- (C₁₋₆ alkyl that may be halogenated) amino group (for example, a methylamino group, a trifluoromethylamino group, a dimethylamino group, an ethylamino group, a diethylamino group, a propylamino group, and a dibutylamino group), a mono- or di-C₂₋₆ alkenyl amino group (for

example, a diallylamino group), a mono- or di-C₃₋₁₀ cycloalkylamino group (for example, a cyclopropylamino group and a cyclohexylamino group), a mono- or di-C₆₋₁₄ arylamino group (for example, a phenylamino group), a mono- or di-C₇₋₁₆ aralkylamino group (for example, a benzylamino group and a dibenzylamino group), a mono- or di- (C₁₋₆ alkyl that may be halogenated)-carbonylamino group (for example, an acetylamino group and a propionylamino group), a mono- or di-C₆₋₁₄ aryl-carbonylamino group (for example, a benzoylamino group), a mono- or di-C₇₋₁₆ aralkyl-carbonylamino group (for example, a benzylcarbonylamino group), a mono- or di- 5- to 14-membered aromatic heterocyclic carbonylamino group (for example, a nicotinoylamino group and an isonicotinoylamino group), a mono- or di- 3- to 14-membered non-aromatic heterocyclic carbonylamino group (for example, a piperidinylcarbonylamino group), a mono- or di-C₁₋₆ alkoxy-carbonylamino group (for example, a tert-butoxycarbonylamino group), a 5- to 14-membered aromatic heterocyclic amino group (for example, a pyridylamino group), a carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl) amino group (for example, a methylcarbamoylamino group), a (mono- or di-C₇₋₁₆ aralkyl-carbamoyl) amino group (for example, a benzylcarbamoyl amino), a C₁₋₆ alkylsulfonylamino group (for example, a methylsulfonylamino group and an ethylsulfonylamino group), a C₆₋₁₄ arylsulfonylamino group (for example, a phenylsulfonylamino group), a (C₁₋₆ alkyl) (C₁₋₆ alkyl-carbonyl) amino group (for example, an N-acetyl-N-methylamino group), and a (C₁₋₆ alkyl) (C₆₋₁₄ aryl-carbonyl) amino group (for example, an N-benzoyl-N-methylamino group).

[0030]

In the present specification, examples of the “carbamoyl group that may be substituted” include a carbamoyl group that may have “one or two substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, that each may have one to three substituents selected from the substituent group A.”

Suitable examples of the carbamoyl group that may be substituted include a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (for example, a diallyl carbamoyl group), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (for example, a cyclopropyl carbamoyl group and a cyclohexylcarbamoyl group), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (for example, a phenylcarbamoyl group), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (for example, an acetylcarbamoyl group

and a propionylcarbamoyl group), a mono- or di-C₆₋₁₄ aryl-carbonyl-carbamoyl group (for example, a benzoylcarbamoyl group), and a 5- to 14-membered aromatic heterocyclic carbamoyl group (for example, a pyridylcarbamoyl group).

[0031]

5 In the present specification, examples of the “thiocarbamoyl group that may be substituted” include a thiocarbamoyl group that may have “one or two substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic
10 carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, that each may have one to three substituents selected from the substituent group A.”

Suitable examples of the thiocarbamoyl group that may be substituted include a thiocarbamoyl
15 group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (for example, a methyl thiocarbamoyl group, an ethyl thiocarbamoyl group, a dimethyl thiocarbamoyl group, a diethyl thiocarbamoyl group, and an N-ethyl-N-methyl thiocarbamoyl group), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (for example, a diallyl thiocarbamoyl group), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (for example, a cyclopropyl thiocarbamoyl group and a cyclohexyl thiocarbamoyl group), a mono- or
20 di-C₆₋₁₄ aryl-thiocarbamoyl group (for example, a phenyl thiocarbamoyl group), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (for example, a benzyl thiocarbamoyl group and a phenethyl thiocarbamoyl group), a mono- or di-C₁₋₆ alkyl-carbonyl-thiocarbamoyl group (for example, an acetyl thiocarbamoyl group and a propionyl thiocarbamoyl group), a mono- or di-C₆₋₁₄ aryl-carbonyl-thiocarbamoyl group (for example, a benzoyl thiocarbamoyl group), and a 5- to 14-
25 membered aromatic heterocyclic thiocarbamoyl group (for example, a pyridyl thiocarbamoyl group).

[0032]

In the present specification, examples of the “sulfamoyl group that may be substituted” include a sulfamoyl group that may have “one or two substituents selected from a C₁₋₆ alkyl group, a C₂₋₆
30 alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, and a mono- or di-C₇₋₁₆ aralkyl-

carbamoyl group, that each may have one to three substituents selected from the substituent group A.”

Suitable examples of the sulfamoyl group that may be substituted include a sulfamoyl group, a mono- or di-C₁₋₆ alkyl-sulfamoyl group (for example, a methyl sulfamoyl group, an ethyl sulfamoyl group, a dimethyl sulfamoyl group, a diethyl sulfamoyl group, and an N-ethyl-N-methyl sulfamoyl group), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (for example, a diallyl sulfamoyl group), a mono- or di-C₃₋₁₀ cycloalkyl-sulfamoyl group (for example, a cyclopropyl sulfamoyl group and a cyclohexyl sulfamoyl group), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (for example, a phenyl sulfamoyl group), a mono- or di-C₇₋₁₆ aralkyl-sulfamoyl group (for example, a benzyl sulfamoyl group and a phenethyl sulfamoyl group), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (for example, an acetyl sulfamoyl group and a propionyl sulfamoyl group), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (for example, a benzoyl sulfamoyl group), and a 5- to 14-membered aromatic heterocyclic sulfamoyl group (for example, a pyridyl sulfamoyl group).

[0033]

In the present specification, examples of the “hydroxy group that may be substituted” include a hydroxy group that may have a “substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclic carbonyl group, a 3- to 14-membered non-aromatic heterocyclic carbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group, and a C₆₋₁₄ arylsulfonyl group that each may have one to three substituents selected from the substituent group A.”

Suitable examples of the hydroxy group that may be substituted include a hydroxy group, a C₁₋₆ alkoxy group, a C₂₋₆ alkenyloxy group (for example, an allyloxy group, a 2-butenyloxy group, a 2-pentenyl group, and a 3-hexenyloxy group), a C₃₋₁₀ cycloalkyloxy group (for example, a cyclohexyloxy group), a C₆₋₁₄ aryloxy group (for example, a phenoxy group and a naphthyloxy group), a C₇₋₁₆ aralkyloxy group (for example, a benzyloxy group and a phenethyloxy group), a C₁₋₆ alkyl-carbonyloxy group (for example, an acetyloxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy, and a pivaloyloxy group), a C₆₋₁₄ aryl-carbonyloxy group (for example, a benzoyloxy group), a C₇₋₁₆ aralkyl-carbonyloxy group (for example, a benzylcarbonyloxy group), a 5- to 14-membered aromatic heterocyclic carbonyloxy group (for example, a nicotinoyloxy group), a 3- to 14-membered non-aromatic heterocyclic carbonyloxy group (for example, a piperidinylcarbonyloxy group), a C₁₋₆ alkoxy-carbonyloxy group (for example, a tert-butoxycarbonyloxy group), 5- to 14-membered aromatic heterocyclic oxy group (for example, a

pyridyloxy group), a carbamoyloxy group, a C₁₋₆ alkyl-carbamoyloxy group (for example, a methyl carbamoyloxy group), a C₇₋₁₆ aralkyl-carbamoyloxy group (for example, a benzylcarbamoyloxy group), a C₁₋₆ alkylsulfonyloxy group (for example, a methylsulfonyloxy group and an ethylsulfonyloxy group), and a C₆₋₁₄ arylsulfonyloxy group (for example, a phenylsulfonyloxy group).

[0034]

In the present specification, examples of the "sulfanyl group that may be substituted" include a sulfanyl group that may have "substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, and a 5- to 14-membered aromatic heterocyclic carbonyl group, that each may have one to three substituents selected from the substituent group A."

Suitable examples of the sulfanyl group that may be substituted include a sulfanyl (-SH) group, a C₁₋₆ alkylthio group, a C₂₋₆ alkenylthio group (for example, an allylthio group, a 2-butenylthio group, a 2-pentenylthio group, and a 3-hexenylthio group), a C₃₋₁₀ cycloalkylthio group (for example, a cyclohexylthio group), a C₆₋₁₄ arylthio group (for example, a phenylthio group and a naphthylthio group), a C₇₋₁₆ aralkylthio group (for example, a benzylthio group and a phenethylthio group), a C₁₋₆ alkyl-carbonylthio group (for example, an acetylthio group, a propionylthio group, a butyrylthio group, an isobutyrylthio group, and a pivaloylthio group), a C₆₋₁₄ aryl-carbonylthio group (for example, a benzoylthio group), a 5- to 14-membered aromatic heterocyclic thio group (for example, a pyridylthio group), a halogenated thio group (for example, a pentafluorothio group).

[0035]

In the present specification, examples of the "silyl group that may be substituted" include a silyl group that may have "one to three substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, and a C₇₋₁₆ aralkyl group, that each may have one to three substituents selected from the substituent group A."

Suitable examples of the silyl group that may be substituted include a tri-C₁₋₆ alkylsilyl group (for example, a trimethylsilyl group and a tert-butyl (dimethyl) silyl group).

[0036]

In the present specification, examples of the "C₁₋₃ alkyl group" include the one with one to three carbon atoms in the "C₁₋₆ alkyl groups."

[0037]

In the present specification, "C₁₋₃ alkyl group that may be substituted with a fluorine atom" means the C₁₋₃ alkyl group that may be substituted with one to five (preferably one to three, more preferably one to two) fluorine atoms.

[0038]

In the present specification, the benzene ring of the "benzene ring that may be further substituted" may have, for example, one to four (preferably one to three, more preferably one to two) substituents selected from the substituent group A.

5 [0039]

In the present specification, among the "benzene ring, pyridine ring, or pyrazine ring that each may be further substituted", the benzene ring may have a substituent similar to the above-mentioned "benzene ring that may be further substituted," the pyridine ring may have, for example, one to three (preferably one to two) substituents selected from the substituent group A, and the
10 pyrazine ring may have, for example, one to two (preferably one) substituents selected from the substituent group A.

[0040]

In the present specification, the pyrimidine ring of the "pyrimidine ring that may be further substituted" may have, for example, one to two (preferably one) substituents selected from the
15 substituent group A.

[0041]

The definition of each symbol in the formula (I) is described in detail below.

R¹ indicates a C₁₋₃ alkyl group that may be substituted with a fluorine atom, or a halogen atom.

R¹ is preferably a C₁₋₃ alkyl group (for example, a methyl group) that may be substituted with
20 one to three (preferably one to two) fluorine atoms, or a halogen atom (for example, a fluorine atom and a chlorine atom).

[0042]

R² indicates a C₁₋₃ alkyl group that may be substituted with a fluorine atom.

R² is preferably a C₁₋₃ alkyl group (for example, a methyl group and an ethyl group) that may be
25 substituted with one to three fluorine atoms. R² is further preferably a C₁₋₃ alkyl group that is not substituted (for example, a methyl group).

[0043]

R³ indicates a hydrogen atom or a hydroxy group.

[0044]

30 The ring A indicates a benzene ring that may be further substituted.

The benzene ring indicated by the ring A may have one to four (preferably one to two) substituents in addition to R¹ and -O-ring B-. Examples of the substituent include a substituent selected from the substituent group A, and it is preferably a halogen atom (for example, a fluorine atom).

35 [0045]

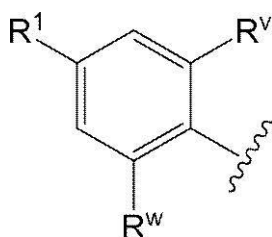
The ring A is preferably a benzene ring that may be further substituted with one to four (preferably one to two) halogen atoms (for example, a fluorine atom). The ring A is further preferably a benzene ring that may be further substituted with one to two (preferably one) halogen atoms (for example, a fluorine atom).

5 [0046]

In one embodiment of the present invention, the ring A is preferably a benzene ring further substituted with a halogen atom (for example, a fluorine atom) at one or two ortho positions with respect to the -O-ring B-, and further preferably, the ring A indicates

[0047]

10 [Chemical Formula 6]



[0048]

(in the formula,

R^I is as defined above;

15 R^V is a halogen atom (for example, a fluorine atom); and

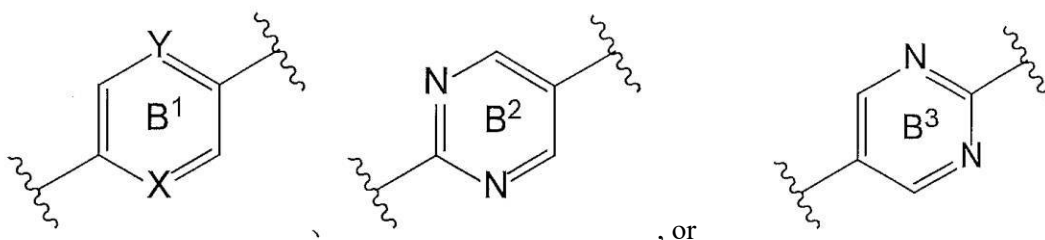
R^W indicates a hydrogen atom or a halogen atom (for example, a fluorine atom)).

[0049]

The ring B indicates

[0050]

20 [Chemical Formula 7]



[0051]

(in the formula, X and Y each independently indicate a carbon atom or a nitrogen atom;

25 the ring B¹ indicates a benzene ring, a pyridine ring, or a pyrazine ring that each may be further substituted; and

the ring B² and ring B³ each indicate a pyrimidine ring that may be further substituted).

[0052]

The benzene ring (X and Y are both carbon atoms), the pyridine ring (either X or Y is a carbon atom, and the other is a nitrogen atom), or the pyrazine ring (X and Y both are nitrogen atoms) indicated by the ring B¹ may have one to four (preferably one to two) substituents. Examples of the substituent include a substituent selected from the substituent group A.

The ring B¹ is preferably a benzene ring (the same as above), a pyridine ring (the same as above), or a pyrazine ring (the same as above) that each is not further substituted.

[0053]

The ring B¹ is further preferably a pyridine ring that is not further substituted, in which either X or Y is a carbon atom, and the other is a nitrogen atom; and particularly preferably, X is a nitrogen atom and Y is a carbon atom.

[0054]

The pyrimidine rings indicated by the ring B² and the ring B³ may have one to two (preferably one) substituents. Examples of the substituent include a substituent selected from the substituent group A.

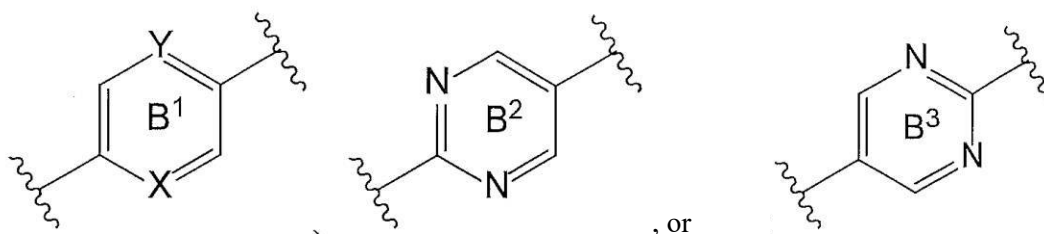
The ring B² and the ring B³ are each preferably a pyrimidine ring that is not further substituted).

[0055]

The ring B preferably indicates

[0056]

[Chemical Formula 8]



[0057]

(in the formula,

X and Y each independently represent a carbon atom or a nitrogen atom;

the ring B¹ indicates a benzene ring, a pyridine ring, or a pyrazine ring that each is not further substituted; and

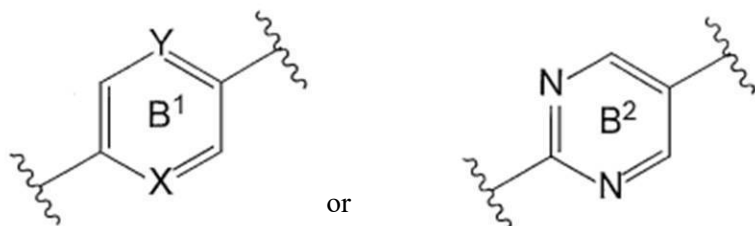
the ring B² and ring B³ each indicate a pyrimidine ring that is not further substituted).

[0058]

The ring B more preferably indicates

[0059]

[Chemical Formula 9]



[0060]

(in the formula,

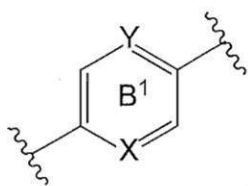
- 5 either X or Y is a carbon atom, and the other is a nitrogen atom;
the ring B¹ indicates a pyridine ring that is not further substituted; and
the ring B² indicates a pyrimidine ring that is not further substituted).

[0061]

The ring B further preferably indicates

10 [0062]

[Chemical Formula 10]



[0063]

(in the formula,

- 15 either X or Y is a carbon atom, and the other is a nitrogen atom (preferably, X is a nitrogen atom,
and Y is a carbon atom); and
the ring B¹ indicates a pyridine ring that is not further substituted).

[0064]

Z indicates CH₂, CF₂, O, or NH.

20 [0065]

In one embodiment of the present invention, Z is preferably CH₂, O, or NH. Z is further preferably CH₂ or O.

[0066]

Suitable examples of the compound (I) include the following compounds.

25 [Compound I-1]

A compound (I), wherein R¹ is a C₁₋₃ alkyl group (for example, a methyl group) that may be substituted with one to three fluorine atoms, or a halogen atom (for example, a fluorine atom and a chlorine atom);

R² is a C₁₋₃ alkyl group (for example, a methyl group and an ethyl group) that may be substituted with one to three fluorine atoms;

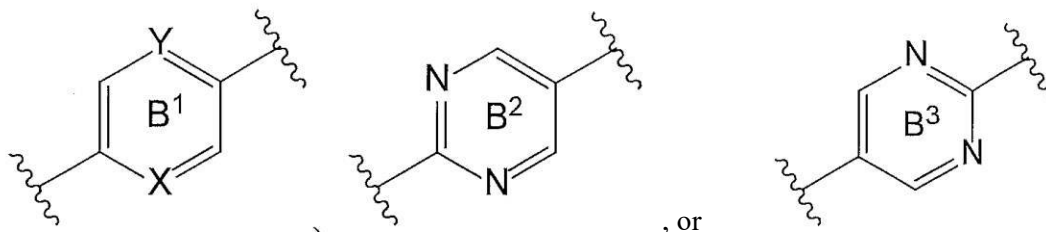
R³ is a hydrogen atom or a hydroxy group;

the ring A is a benzene ring that may be further substituted with one to four (preferably one to two) halogen atoms (for example, a fluorine atom);

the ring B is

[0067]

[Chemical Formula 11]



[0068]

;

X and Y each independently indicate a carbon atom or a nitrogen atom;

the ring B¹ is a benzene ring, a pyridine ring, or a pyrazine ring that each is not further substituted;

the ring B² and ring B³ each indicate a pyrimidine ring that is not further substituted; and

Z is CH₂, CF₂, O, or NH.

[0069]

[Compound I-2]

The compound (I) wherein R¹ is a C₁₋₃ alkyl group (for example, a methyl group) that may be substituted with one to two fluorine atoms, or a halogen atom (for example, a fluorine atom and a chlorine atom);

R² is a C₁₋₃ alkyl group that is not substituted (for example, a methyl group);

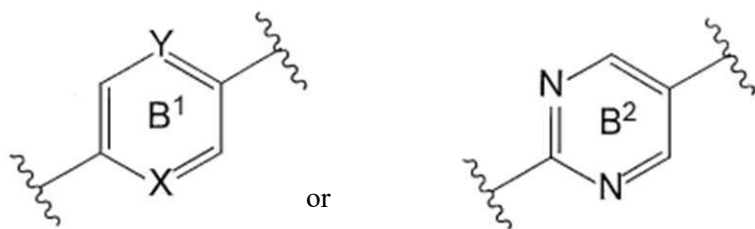
R³ is a hydrogen atom or a hydroxy group;

the ring A is a benzene ring that is further substituted with one to two (preferably one) halogen atoms (for example, a fluorine atom);

the ring B is

[0070]

[Chemical Formula 12]



[0071]

;

either X or Y is a carbon atom, and the other is a nitrogen atom (preferably, X is a nitrogen atom,
5 and Y is a carbon atom);

the ring B¹ is a pyridine ring that is not further substituted;

the ring B² is a pyrimidine ring that is not further substituted; and

Z is CH₂ or O.

[0072]

10 [Compound I-3]

The compound (I) wherein R¹ is a C₁₋₃ alkyl group (for example, a methyl group) that may be substituted with one to two fluorine atoms, or a halogen atom (for example, a fluorine atom and a chlorine atom);

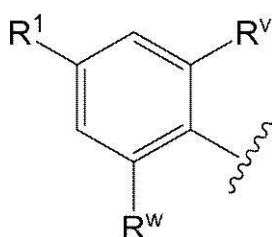
R² is a C₁₋₃ alkyl group that is not substituted (for example, a methyl group);

15 R³ is a hydrogen atom or a hydroxy group;

the ring A is

[0073]

[Chemical Formula 13]



20 [0074]

;

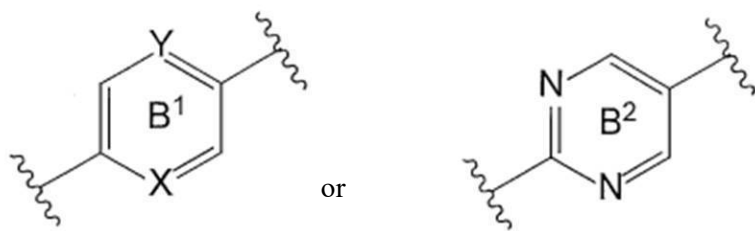
R^v is a halogen atom (for example, a fluorine atom);

R^w is a hydrogen atom or a halogen atom (for example, a fluorine atom);

the ring B is

25 [0075]

[Chemical Formula 14]



[0076]

;

either X or Y is a carbon atom, and the other is a nitrogen atom (preferably, X is a nitrogen atom, and Y is a carbon atom);

the ring B¹ is a pyridine ring that is not further substituted;

the ring B² is a pyrimidine ring that is not further substituted; and

Z is CH₂ or O.

[0077]

Specific examples of the compound (I) include compounds of the following examples 1 to 16 and 18 to 50.

[0078]

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

[0079]

Suitable examples of the salt with an inorganic base include an alkaline metal salt such as a sodium salt and a potassium salt; an alkaline earth metal salt such as a calcium salt and a magnesium salt; an aluminum salt; or an ammonium salt.

[0080]

Suitable examples of the salt with an organic base include a salt with trimethylamine, triethylamine, pyridine, picolin, ethanolamine, diethanolamine, triethanolamine, trometamine [tris (hydroxymethyl) methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, or N,N-dibenzylethylenediamine.

[0081]

Suitable examples of the salt with an inorganic acid include a salt with hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, or phosphoric acid.

[0082]

Suitable examples of the salt with an organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, or p-toluenesulfonic acid.

[0083]

- 5 Suitable examples of the salt with a basic amino acid include a salt with arginine, lysine, or ornithine.

[0084]

Suitable examples of the salt with an acidic amino acid include a salt with aspartic acid or glutamic acid.

- 10 [0085]

The compound (I) may be used as a prodrug.

- The prodrug of the compound (I) is a compound which is converted into the compound (I) by reaction with an enzyme, a stomach acid, and the like, under physiological conditions in a living body, that is, a compound which is changed into the compound (I) by enzymatic oxidation,
15 reduction, hydrolysis, and the like, and it is a compound which is changed into the compound (I) by hydrolysis by the stomach acid and the like.

[0086]

Examples of the prodrug of the compound (I) include:

- a compound in which the amino group of the compound (I) is acylated, alkylated, or
20 phosphorylated (for example, a compound in which the amino group of the compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl) methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, or tert-butylated);

- a compound in which the hydroxy group of the compound (I) is acylated, alkylated,
25 phosphorylated, or borated (for example, a compound in which the hydroxy group of the compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, allanylated, or dimethylaminomethylcarbonylated); a compound in which the carboxy group of the compound (I) is esterified or amidated (for example, a compound in which the carboxy group of the compound (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified,
30 dimethylaminomethyl esterified, pivaloyloxy methyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl esterified, cyclohexyloxycarbonylethyl esterified, or methylamidated); and the like. These compounds may be produced from the compound (I) by a method known per se.

[0087]

In addition, the prodrug of the compound (I) may be changed to the compound (I) under physiological conditions as described in the page 163 to page 198 of Molecular Design of the seventh volume of "Development of Medicine" published in 1990 by Hirokawa Shoten.

In the present specification, the prodrug may form a salt, and examples of such a salt include the one exemplified as the salt of a compound indicated by the formula (I) described above.

[0088]

In addition, the compound (I) may be labeled by an isotope (for example, ^3H , ^{13}C , ^{14}C , ^{18}F , ^{35}S , and ^{125}I) and the like.

The compound (I) labeled by or substituted with an isotope may be used, for example, as a tracer in the positron emission tomography (Positron Emission Tomography: PET) (PET tracer), and can be useful in fields such as medical diagnosis.

Furthermore, the compound (I) may be a hydrate, a non-hydrate, a non-solvate, or a solvate.

Furthermore, the compound (I) also includes a heavy hydrogen conversion product obtained by converting ^1H to ^2H (D).

Furthermore, the compound (I) may be a pharmaceutically acceptable co-crystal or co-crystal salt. Here, the co-crystal or the co-crystal salt means a crystalline substance composed of two or more types of unique solids at room temperature, each having different physical properties (for example, structure, melting point, melting heat, hygroscopicity, solubility, and stability). The co-crystal or the co-crystal salt may be produced according to a co-crystallization method known per se.

[0089]

The compound (I) or the prodrug thereof (hereinafter, it may be simply abbreviated as the compound of the present invention) can be used as a preventive or therapeutic agent for various diseases described below for mammals (for example, humans, mice, rats, rabbits, dogs, cats, cows, horses, pigs, and monkeys) as is or by forming a pharmaceutical composition (in the present specification, it may be abbreviated as the "compound of the present invention") by mixing with a pharmaceutically acceptable carrier or the like.

[0090]

As the pharmacologically acceptable carrier, various organic or inorganic carrier materials used as the formulation materials can be used, and it can be blended as an excipient, a lubricant, a binder, or a disintegrant in a solid formulation; a solvent, a solubilization agent, a suspending agent, a tonicity agent, a buffer, or a soothing agent in a liquid formulation; or the like. In addition, a formulation additive such as a preservative, an antioxidant, a colorant, or a sweetener can be used as necessary.

[0091]

Suitable examples of the excipient include lactose, white sugar, D-mannitol, D-sorbitol, starch, α starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, carboxymethylcellulose sodium, gum arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, and magnesium aluminometasilicate.

5 [0092]

Suitable examples of the lubricant include magnesium stearate, calcium stearate, talc, and colloidal silica.

[0093]

10 Suitable examples of the binder include α starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, crystalline cellulose, white sugar, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone.

[0094]

15 Suitable examples of the disintegrating agent include lactose, white sugar, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, light anhydrous silicic acid, and low-substitution hydroxypropylcellulose.

[0095]

20 Suitable examples of the solvent include water for injection, physiological saline, Ringer's fluid, alcohol, propylene glycol, polyethylene glycol, sesame seed oil, corn oil, olive oil, and cotton seed oil.

[0096]

25 Suitable examples of the solubilization agent include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, and sodium acetate.

[0097]

30 Suitable examples of the suspending agent include a surfactant such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, and glyceryl monostearate; a hydrophilic high molecule such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose; polysorbates, and polyoxyethylene hydrogenated castor oil.

[0098]

35 Suitable examples of the isotonic agent include sodium chloride, glycerin, D-mannitol, D-sorbitol, and glucose.

[0099]

Suitable examples of the buffer agent include a buffer solution such as a phosphate, an acetate, a carbonate, and a citrate.

Suitable examples of the soothing agent include benzyl alcohol.

5 [0100]

Suitable examples of the preservative include para-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, and sorbic acid.

Suitable examples of the antioxidant include sulfite and ascorbate.

[0101]

10 Suitable examples of the colorant include a water-soluble edible tar dye (for example, a food coloring such as edible red No. 2 and No. 3, edible yellow No. 4 and No. 5, and edible blue No. 1 and No. 2), a water-insoluble lake dye (for example, an aluminum salt of the water-soluble edible tar dye), a natural dye (for example, β -carotene, chlorophyll, and Bengala dye).

[0102]

15 Suitable examples of the sweetener include saccharin sodium, dipotassium glycyrrhizinate, aspartame, and stevia.

[0103]

Examples of the pharmaceutical dosage form of the present invention include an oral formulation such as a tablet (including a sugar-coated tablet, a film-coated tablet, a sublingual tablet, an oral
20 disintegrating tablet, a buccal tablet, and the like), a pill, a powder, a granules, a capsule (including a soft capsule and a microcapsule), a troche, a syrup, a liquid, an emulsion, a suspension agent, an aerosol, a film (for example, an oral disintegrating film and an oral mucosal patch); and a parenteral formulation such as an injection (for example, a subcutaneous injection, an intravenous injection, an intramuscular injection, an intraperitoneal injections, and infusion), a topical agent (for
25 example, a transdermal formulation, an ointment, a lotion, and a patch), a suppository (for example, a rectal suppository and a vaginal suppository), a pellet, a parenteral agent, a transpulmonary agent (inhalant), and an eye drop. The compound of the present invention and the pharmaceutical of the present invention can be administered orally or parenterally (for example, intravenous, intraarterial, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, instillation,
30 intracerebral, endorectal, intravaginal, intraperitoneal, intratumoral, and near-tumor administrations and the like and administration directly to lesions).

[0104]

These formulations may be controlled-release formulations such as quick release formulations or sustained release formulations (for example, a sustained release microcapsule).

35 [0105]

The pharmaceutical of the present invention can be produced by a method commonly used in the pharmaceutical technology field, for example, the method described in the Japanese Pharmacopoeia.

[0106]

5 It should be noted that the content of the compound of the present invention in the pharmaceutical of the present invention may be, for example, about 0.1 to 100 wt% although it depends on the dosage form, the dosage of the compound of the present invention, and the like.

[0107]

10 When an oral agent is produced, coating may be carried out for the purpose of masking the taste, an enteric property, or durability.

[0108]

Examples of the coating base used for coating include a sugar coating base, a water-soluble film coating base, an enteric film coating base, and a sustained-release film coating base.

[0109]

15 White sugar is used as the sugar coating base, and moreover, one or more types selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, and Carnauba wax may be used together.

[0110]

20 Examples of the water-soluble film coating base include a cellulose-based high molecule such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, and methylhydroxyethylcellulose; a synthetic high molecule such as polyvinyl acetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trade name)], and polyvinylpyrrolidone; and a polysaccharide such as pullulan.

[0111]

25 Examples of the enteric film coating base include a cellulose-based high molecule such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, and cellulose phthalate acetate; an acrylate-based high molecule such as methacrylate copolymer L [Eudragit L (trade name)], methacrylate copolymer LD [Eudragit L-30D55 (trade name)], and methacrylate copolymer S [Eudragit S (trade name)]; and a
30 natural product such as shellac.

[0112]

35 Examples of the sustained-release film coating base include a cellulose-based high molecule such as ethyl cellulose; and an acrylate-based high molecule such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name)] and ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)].

[0113]

The coating bases described above may be used by mixing two or more types of the coating base in an appropriate ratio. In addition, a light shielding agent such as titanium oxide and iron sesquioxide may be used for coating.

5 [0114]

The compound of the present invention has an antagonistic effect of the NMDA receptor containing the NR2B subunit. Here, the antagonistic action of the NMDA receptor containing the NR2B subunit is confirmed, for example, by an suppressing effect on activation of the receptor (for example, intracellular calcium ion (Ca^{2+}) inflow by glutamic acid).

10 It should be noted that the NMDA receptor containing the NR2B subunit is a receptor containing one NR2B subunit

and further composed of four subunits in total including three subunits of two to three types selected from NR1, NR2A, NR2B, NR2C, NR2D, NR3A, and NR3B.

15 The NMDA receptor containing the NR2B subunit is preferably a receptor composed of four subunits consisting of a hetero dimer of NR1 and NR2B, one type of subunit selected from NR2A, NR2B, NR2C, and NR2D, and a hetero dimer of NR1.

The NMDA receptor containing the NR2B subunit is more preferably a receptor composed of four subunits consisting of two sets of hetero dimers of NR1 and NR2B.

20 In addition, the compound of the present invention is expected to be low in toxicity (for example, cardiotoxicity, acute toxicity, chronic toxicity, genotoxicity, reproductive toxicity, pulmonary toxicity, and carcinogenicity) and to have less side effects (for example, psychotomimetic side effect (psychotomimetic side effect)), and can be used as a preventive agent or a therapeutic agent or diagnostic agent for various diseases to mammals.

25 The compound of the present invention is expected to have low mutagenicity in Ames tests (Ames tests) and low hERG (human ether-a-go-go-related gene) inhibition effect. In addition, it is expected that the compound of the present invention has a small amount of extracerebral discharge via the BCRP (breast cancer resistance protein) transporter and is excellent in stability against conjugated metabolism.

The compound of the present invention is expected to have excellent intracerebral transferability.

30 [0115]

The compound of the present invention can be used as a preventive or therapeutic agent for central and peripheral diseases. The compound of the present invention can be useful as a preventive or therapeutic agent for various diseases, such as

35 (1) mental illness (for example, major depression (including refractory major depression and treatment-resistant depression), minor depressive

disorder, bipolar depression, recurrent depression, postpartum depression, stress disorder, major depressive disorder associated with psychosis (including delusional disorder and schizophrenia), manic or mixed mood episodes, mild manic mood episodes, depression episodes with atypical features, depression episodes with melancholy features, depression episodes with tension characteristics, post-stroke depression episodes (hereinbefore, these may simply be referred to as "depression" in the present specification), dysthymic disorder, affective disorder (seasonal affective disorder, and the like), delirium, dementia peripheral symptoms (psychiatric symptoms or behavioral abnormalities), anxiety, generalized anxiety disorder, anxiety syndrome, mood disorder, mood circulation disorder, premenstrual dysphoric mood disorder, panic disorder, phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, psychic post-traumatic stress syndrome, post-traumatic stress disorder, paranoid or depressive schizoaffective disorder, paranoid personality disorder, Tourette syndrome, autism, fragile X syndrome, Rett syndrome, adjustment disorder, bipolar disorder (including type I bipolar disorder and type II bipolar disorder), neurosis, schizophrenia (for example, positive symptoms, negative symptoms, memory loss, paranoid schizophrenia, disassembled schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, and residual schizophrenia), schizophrenia-like disorders, chronic fatigue syndrome, anxiety neurosis, obsessive-compulsive neurosis, panic disorder, epilepsy, pediatric refractory epilepsy syndrome, West syndrome, anxiety symptoms, discomfort psychosis, emotional abnormalities, emotional circulation, nerve hypersensitivity, fainting, indulgence, decreased libido, attention deficit hyperactivity disorder (ADHD), psychotic disorders (for example, short-term psychotic disorders and shared psychotic disorders), alcohol-, amphetamines-, cannabis-, cocaine-, hallucinogens-, obesity-, inhalants-, opioids-, or phencyclidine-induced psychosis, delusional disorder, Noonan syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann syndrome, Silver Russell syndrome, nodular sclerosis, Williams syndrome, Kallman syndrome, and Rubinstein-Taybi syndrome], movement disorder, mental retardation, paranoia,

(2) neurodegenerative disease [for examples, Alzheimer's disease, Alzheimer's type senile dementia, Parkinson's disease, Huntington's chorea, multiple cerebral infarction dementia, frontal-temporal dementia, Parkinson's type frontal dementia, alcoholic dementia, or other drug-related dementia, dementia associated with intracranial tumor or brain trauma, dementia associated with Huntington's disease or Parkinson's disease, neurodegeneration associated with brain trauma, neurodegeneration associated with stroke, neurodegeneration associated with cerebral infarction, neurodegeneration associated with hypoglycemia, neurodegeneration associated with epilepsy, neurodegeneration associated with neurotoxicity, multisystem atrophy, spinal cord injury, AIDS-related dementia, progressive nuclear paralysis, Pick syndrome, Niemann-Pick syndrome,

corticobasal degeneration, Down syndrome, vascular dementia, Parkinson's disease after encephalitis, Lewy body dementia, HIV dementia, amyotrophic lateral sclerosis (ALS), motor neurogenic disease (MND), Kreuzfeld-Jakob disease or prion disease, cerebral palsy, progressive supranuclear palsy, multiple sclerosis, and neuromyopathy],

5 (3) amnesic disorder, mild cognitive impairment, learning disorder (for example, reading disorder, math disorder, and disorder of written expression), and cognitive and memory impairment with aging [for example, age-related memory impairment and senile dementia],

(4) sleep disorder [for example, intrinsic sleep disorder (for example, psychophysiological insomnia, and the like), extrinsic sleep disorder, circadian rhythm disorder (for example, time zone
10 change syndrome (jet lag), shift work sleep disorder, irregular sleep-wake pattern, sleep phase recession syndrome, sleep phase advance syndrome, non-24-hour sleep awakening, and the like), parasomnia, sleep disorder associated with internal or psychiatric disorder (for example, chronic obstructive pulmonary disease, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, schizophrenia, depression, and anxiety neurosis), stress insomnia, insomnia, insomnia
15 neurosis, and sleep apnea syndrome],

(5) respiratory depression due to anesthetics, traumatic diseases, neurodegenerative diseases, or the like,

(6) pain [for example, psychogenic pain (physical expression disorder, pain disorder, somatization disorder, hypochondria, conversion disorder, and chronic pain with depression), inflammatory
20 pain, peripheral neuropathic pain, central neuropathic pain, neuropathic pain, acute pain, refractory pain, cancerous persistent pain, cancerous breakthrough pain, cancerous pain, persistent pain, physical pain, breakthrough pain, chronic pain, tenderness, general pain, dull pain, skin pain disease, radiating pain, pain, and postthoracotomy pain syndrome],

(7) deafness [for example, kanamycin deafness, streptomycin deafness, addictive deafness, senile
25 deafness, idiopathic bilateral sensorineural deafness, sudden deafness, acquired deafness, hereditary deafness, organic deafness, treble-impaired deafness, occupational hearing loss, occupational deafness, and bass-impaired deafness],

(8) traumatic brain injury and associated disorder or complication thereof, post-concussion syndrome, infant shake syndrome, stroke, age-related macular degeneration, eye palatal tremor,
30 spasm, phantom limb pain, radiation lethargic syndrome, nervous loss of appetite, eating disorder, nervous anorexia, hyperphagia, other eating disorders, alcoholism, alcohol abuse, alcoholic forgetfulness, alcohol delusions, alcohol preference, alcohol withdrawal, alcoholic psychosis, alcohol poisoning, alcoholic jealousy, alcoholic manic psychosis, alcohol dependence mental disorder, alcohol psychosis, hepatic encephalopathy, drug preference, drug phobia, drug enthusiast,
35 drug abuse, drug dependence, drug withdrawal, migraine (migraine, migraine), stress headache,

tension headache, diabetic neuropathy, obesity, diabetes, muscle spasm, Meniere's disease, autonomic imbalance, alopecia, glaucoma, hypertension, heart disease, tachycardia, congestive heart failure, hyperventilation, bronchial asthma, anaerobiosis, sudden infant death syndrome, inflammatory disease, allergic disease, systemic erythematodes, impotence, menopausal disorder, infertility, cancer, immunodeficiency syndrome due to HIV infection, immunodeficiency syndrome due to stress, cerebrospinal fever, terminal hypertrophy, incontinence, metabolic syndrome, osteoporosis, digestive ulcer, irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, stress gastrointestinal disorder, nervous vomiting, diarrhea, constipation, and postoperative ileus.

[0116]

In particular, the compound of the present invention can be useful for the prevention or treatment of depression (including major depression, refractory depression, treatment-resistant depression, and the like), bipolar disorder, migraine, pain, or peripheral symptoms of dementia.

Both depression and bipolar disorder are categorized as mood disorders and are disorders that exhibit a depressive state, or a depressive state and a manic state for a long period of time. In recent years, it has been found that the intravenous single administration of ketamine, an NMDA receptor antagonist, rapidly and continuously improves depression symptoms associated with major depression and bipolar disorder [Therapeutic Advances in Psychopharmacology (Ther. Adv. Psychopharmacol.) Vol. 4, page 75 to 99, 2014]. In addition, it has been reported that the treatment-resistant depression symptoms are significantly improved by intravenous continuous administration of CP-101,606 which is an antagonist to the NMDA receptor containing the NR2B subunit [Journal of Clinical Psychopharmacology (J.

Clin. Psychopharmacol.) Vol. 28, page 631 to 637, 2008]. Therefore, the compound of the present invention is promising as a preventive or therapeutic agent for treatment-resistant depression.

[0117]

A migraine is a chronic and paroxysmal primary headache. The underlying mechanism is unknown, but it is thought to occur along with abnormalities of central nervous system processing, abnormalities of the trigeminal neurovascular system, or the like. In the study of the pathophysiological process of migraines, especially of symptoms, the phenomenon of cortical spreading depression (cortical spreading depression) is noted. In an experimental cortical spreading depression test using rodents, it has been reported that CP-101,606 and Ro25-6981, which are antagonists for the NMDA receptor containing the NR2B subunit, suppress the number of occurrences of and the depth of cortical spreading depression [The Journal of Pharmacology and

Experimental Therapeutics (J. Pharmacol. Exp. Ther.) Vol. 321, page 564 to 572, 2007]. Therefore, the compound of the present invention is promising as a preventive or therapeutic agent for migraines.

[0118]

5 Pain is classified into acute pain, in which the pain is sustained for a relatively short period of time, and into chronic pain in which the pain is sustained for three months or longer or reoccurs, the pain is sustained for more than a month after recovery of acute tissue damage, or an accompanying lesion which is not cured is observed. The NMDA receptor containing the NR2B subunit is highly expressed in the posterior horn of the spinal cord which plays an important role
10 in the reception of pain, and it is suggested that the pain may be controlled by the functional control thereof. In fact, it has been reported that the pain threshold value is increased by gene modification operation which causes the lowering of the function of the NR2B subunit [European Journal of Neuroscience (Eur. J. Neurosci.) Vol. 32, page 798 to 810, 2010], and it has reported that the pain
15 threshold value is increased by Ifenprodil, which is an antagonist of the NMDA receptor containing the NR2B subunit [Pain (Pain), Vol. 153, page 1022 to 1029, 2012]. Therefore, the compound of the present invention is promising as a preventive or therapeutic agent for pain.

[0119]

Dementia is a chronic, general, and usually irreversible decline in cognitive ability. The lowering of the quality of life of the patient caused by a decrease in cognitive ability is notable, but peripheral
20 symptoms of dementia (mental symptoms or behavioral abnormalities) are also considered to be a significant factor in the lowering of the quality of life of the patient or the caregiver. Although there is no effective therapeutic intervention for the peripheral symptoms of dementia, it has been reported that the peripheral symptoms of dementia are partially ameliorated by the administration of memantine, an antagonist of the NMDA receptor [The Annals of Pharmacotherapy (Ann.
25 Pharmacother.) Vol. 42, page 32 to 38, 2007]. The NMDA receptors containing the NR2B subunits are widely distributed throughout the brain regions other than the cerebellum, but the peripheral symptoms of dementia are reported to be related to white matter abnormalities in brain regions other than the cerebellum [Journal of the Neurological Sciences (J. Neurol. Sci.) Vol. 337, page
162 to 166, 2014]. Therefore, the compound of the present invention is promising as a preventive
30 or therapeutic agent for peripheral symptoms of dementia.

[0120]

The dosage of the compound of the present invention can be different depending on the object of administration, route of administration, target disease, symptoms, or the like, but, for example, when oral or parenteral administration is carried out to an adult patient, the usual amount for a
35 single time can be about 0.01 to 100 mg/kg of body weight, preferably 0.1 to 50 mg/kg of body

weight, and more preferably 0.5 to 20 mg/kg of body weight, and the amount can be administered once to three times a day.

[0121]

The compound of the present invention can be used in combination with other active ingredients (hereinafter, it is abbreviated as a concomitant drug).

Examples of the concomitant drug includes the following drugs. An acetylcholinesterase inhibitor (for example, donepezil, rivastigmine, galantamine, and zanapezil), a nootropic (for example, memantine), a β -amyloid protein production, secretion, accumulation, aggregation, and/or deposition suppressor, a β -secretase inhibitor (for example, 6-(4-biphenyl) methoxy-2-[2-(N,N-dimethylamino) ethyl] tetraline, 6-(4-biphenyl) methoxy-2-(N,N-dimethylamino) methyltetraline, 6-(4-biphenyl) methoxy-2-(N,N-dipropylamino) methyltetraline, 2-(N,N-dimethylamino) methyl-6-(4'-methoxybiphenyl-4-yl) methoxytetraline, 6-(4-bifeniryl) methoxy-2-[2-(N,N-diethylamino) ethyl] tetraline, 2-[2-(N,N-dimethylamino) ethyl]-6-(4'-methylbiphenyl-4-yl) methoxytetraline, 2-[2-(N,N-dimethylamino) ethyl]-6-(4'-methoxybiphenyl-4-yl) methoxytetraline, 6-(2',4'-dimethoxybiphenyl-4-yl) methoxy-2-[2-(N,N-dimethylamino) ethyl] tetraline, 6-[4-(1,3-benzodioxol-5-yl) phenyl] methoxy-2-[2-(N,N-dimethylamino) ethyl] tetraline, 6-(3',4'-dimethoxybiphenyl-4-yl) methoxy-2-[2-(N,N-dimethylamino) ethyl] tetraline, an optical active substance thereof, a salt thereof, and a hydrate thereof, and OM99-2 (WO 01/00663)), a γ -secretase inhibitor, a β -amyloid protein aggregation inhibitor (for example, PTI-00703, ALZHEMED (NC-531), PPI-368 (JP H11-514333 T), PPI-558 (JP 2001-500852 T), SKF-74652 (Biochem. J. (1999), 340 (1), 283-289)), a brain function activator such as a β -amyloid vaccine and a β -amyloid degrading enzyme, (for example, aniracetam and nicergoline), a therapeutic for Parkinson's disease [(for example, a dopamine receptor agonist (for example, L-dopa, bromocriptine, pergolide, talipexole, pramipexole, cabergoline, and amantadine), a monoamyloid oxidase (MAO) inhibitor (for example, deprenil, selegiline (selegiline), remasemide, and riluzol), an anticholinergic agent (for example, trihexyphenidyl and biperiden), a COMT inhibitor (for example, entacapone)], a therapeutic agent for amyotrophic lateral sclerosis (for example, a neurotrophic factor such as riluzol), a therapeutic agent for abnormal behavior associated with the progression of dementia, wandering, and the like (for example, a sedative and an anxiolytic), an apoptosis inhibitor (for example, CPI-1189, IDN-6556, and CEP-1347), nerve differentiation / regeneration promoter (for example, leteprinin, xaliproden (xaliproden; SR-57746-A), SB-216763, Y-128, VX-853, prosaptide, 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl] isoindoline, 5,6-dimethoxy-2-[3-(4-isopropylphenyl)-2,2,4, 6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl] isoindoline, 6-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]

dioxolo [4,5-f] isoindole and an optically active substance thereof, a salt thereof, and a hydrate thereof), a non-steroidal anti-inflammatory drug (meloxicam, tenoxicam, indomethacin, ibuprofen, celecoxib, rofecoxib, aspirin, indomethacin, and the like), a steroid drug (dexamethasone, hexestrol, cortisone acetate, and the like), disease-modifying antirheumatic drugs (DMARDs), an anti-cytokine drug (for example, a TNF inhibitor and a MAP kinase inhibitor), a therapeutic agent for urinary incontinence / frequent urine (for example, flavoxate hydrochloride, oxybutinine hydrochloride, and propiverine hydrochloride), a phosphodiesterase inhibitor (for example, sildenafil (citrate)), a dopamine agonist (for example, apomorphine), an anti-arrhythmic drug (for example, mexiletine), a sex hormone or a derivative thereof (for example, progesterone, estradiol, and estradiol benzoate), a therapeutic agent for osteoporosis (for example, alfacalcidol, calcitriol, elcatonin, salmon calcitonin, estriol, ipriflavone, disodium pamidronate, sodium alendronate hydrate, and disodium Incadronate), parathyroid hormone (PTH), a calcium receptor antagonist, a therapeutic agent for insomnia (for example, a benzodiazepine drug, a non-benzodiazepine drug, a melatonin agonist, and an orexin receptor antagonist), a schizophrenia drug (for example, a typical antipsychotic such as haloperidol; an atypical antipsychotic such as clozapine, olanzapine, risperidone, and aripiprazole; a drug that affects the metabolic glutamate receptor or the ion channel conjugated glutamate receptor; and a phosphodiesterase inhibitor), a benzodiazepine drug (chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, alprazolam, and the like), an L-type calcium channel inhibitor (pregabalin and the like), a tricyclic or tetracyclic antidepressant drug (imipramine hydrochloride, amitriptyline hydrochloride, clomipramine hydrochloride, mianserin hydrochloride, setiptiline maleate salt, and the like), a selective serotonin reuptake inhibitor (fluvoxamine maleate, fluoxetine hydrochloride, citalopram hydrobromide, escitalopram oxalate, sertraline hydrochloride, paroxetine hydrochloride hydrate, and the like), a serotonin-noradrenaline reuptake inhibitor (venlafaxine hydrochloride, duloxetine hydrochloride, desvenlafaxine, and the like), a noradrenaline reuptake inhibitor (reboxetine mesylate and the like), mirtazapine, trazodone hydrochloride, bupropion hydrochloride, a 5-HT_{1A} agonist (buspirone hydrochloride, tandospirone citrate, osetozotan hydrochloride, and the like), a 5-HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, a 5-HT₃ antagonist (cyamemazine and the like), a non-cardiac-selective β -inhibitor (propranolol hydrochloride, oxprenolol hydrochloride, and the like), a histamine H₁ antagonist, a CRF antagonist, other anti-anxiety agents (meprobamate and the like), a tachykinin antagonist, a drug that affect to the metabolic glutamate receptor, a CCK antagonist, a β 3 adrenaline antagonist (amibegron hydrochloride and the like), a GAT-1 inhibitor, an N-type calcium channel inhibitor, a type-2 carbonate dehydrogenase inhibitor, a NMDA glycine site agonist, a NMDA antagonist (memantine, ketamine, amphetamine, and the like), a peripheral benzodiazepine receptor agonist,

a vasopressin receptor antagonist, a phosphodiesterase inhibitor, an opioid antagonist, an opioid agonist, uridine, a nicotinic acid receptor agonist, thyroid hormone, thyroid stimulating hormone (TSH), thyroid stimulating hormone releasing hormone (TRH), a MAO inhibitor (phenelzine sulfate, tranlycypromine sulfate, moclobemide, and the like), a bipolar disorder therapeutic agent (lithium carbonate, sodium valproate, lamotrigine, riluzole, felbamate, and the like), a cannabinoid CB1 antagonist, a FAAH inhibitor, a sodium channel inhibitor, an anti-ADHD drug (methylphenidate hydrochloride, methamphetamine hydrochloride, and the like), an alcoholism drug, an autism drug, a chronic fatigue syndrome drug, a spasm drug, a fibromyalgia drug, a headache drug, a drug for smoking cessation, a myasthenia gravis drug, a cerebral infarction drug, a mania drug, a hypersomnia drug, a pain drug, a dysthymia drug, an autonomic imbalance drug, a drug for male and female sexual dysfunction, a migraine drug, a drug for pathological gambling, a lower limb immobility syndrome drug, a substance addiction drug, a drug for alcohol-related disease, a drug for hypersensitivity bowel syndrome, a lipid disorder drug such as cholesterol-lowering drug (statins and the like), fibrates, and a squalane synthesis inhibitor), an abnormal behavior drug or a suppressing agent for wandering habits due to dementia (a sedative, an anti-anxiety drug, and the like), an anti-obesity drug, an antidiabetic drug, a drug for diabetic complication, a hypertension drug, a hypotension drug, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antithrombotic agent, an anticancer agent, an antibody drug, a nucleic acid or a nucleic acid derivative, an aptamer drug, and the like.

[0122]

The concomitant drugs described above may be used by combining two or more types at an appropriate ratio.

Furthermore, when the compound of the present invention is applied to each of the diseases described above, the compound can be used in combination with a biological formulation (for example, an antibody drug, a nucleic acid or a nucleic acid derivative, an aptamer drug, and a vaccine formulation), and it can be used in combination with a gene therapy and the like, or it can be also used in combination with a treatment in a psychiatric area without drugs.

Examples of the treatment in a psychiatric area without drugs include a modified electroconvulsive therapy, a deep brain stimulation therapy, a repeated transcranial magnetic stimulation therapy, and a psychotherapy including cognitive behavioral therapy.

In addition, the compound of the present invention can be used in combination with various organ regeneration methods such as cardiac regeneration, renal regeneration, pancreatic regeneration, and vascular regeneration, a cell transplantation therapy using bone marrow cells (marrow mononuclear cell and marrow stem cell), and artificial organs (for example, artificial blood vessel and cardiac muscle cell sheet) using tissue engineering.

[0123]

By combining the compound of the present invention with a concomitant drug,

(1) the dosage can be reduced as compared with the case of the single administration of the compound of the present invention or the concomitant drug,

5 (2) depending on the symptoms of patient (mild, severe, or the like), the compound of the present invention and the concomitant drug can be selected,

(3) the treatment period can be set to a long period by selecting a concomitant drug having a different mechanism of action from the compound of the present invention,

10 (4) the therapeutic effect can be sustained by selecting a concomitant drug having a different mechanism of action from the compound of the present invention, and

(5) by using the compound of the present invention and the concomitant drug in combination, excellent effects such as a synergistic effect can be obtained.

[0124]

15 Hereinafter, the combined use of the compound of the present invention and the concomitant drug is referred to as the "combination agent of the present invention".

When using the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not limited, and the compound of the present invention or the pharmaceutical composition thereof and the concomitant drug or the pharmaceutical composition thereof may be simultaneously administered to the administration
20 subject (the compound of the present invention and the concomitant drug may be administered as a single formulation or as separate formulations), or may be administered at different times. In the case of administering at a difference time, for the order of administration, either of the compound of the present invention or the concomitant drug may be administered earlier. Moreover, the compound of the present invention may be administered after continuously administering the
25 concomitant drug for a fixed period.

The dosage of the concomitant drug may be based on the dosage clinically used, and may be appropriately selected depending on the administration target, administration route, disease, combination, and the like.

30 The dosage of the concomitant drug may be selected as appropriate based on the dosage clinically used. Further, the blending ratio of the compound of the present invention and the concomitant drug may be appropriately selected according to the administration target, administration route, target disease, symptoms, combination, and the like.

[0125]

The method for producing the compound of the present invention is described below.

35 [0126]

The raw materials and reagents used in each step in the following production method and the obtained compounds may each form a salt. Examples of such a salt include a salt similar to the salt of the compound of the present invention described above, and the like.

[0127]

- 5 When the compound obtained in each step is a free compound, the compound may be converted into the target salt by a method known per se. Conversely, when the compound obtained in each step is a salt, the compound may be converted into a free body or other type of salt of object by a method known per se.

[0128]

- 10 The compound obtained in each step may be used in the next reaction as the reaction liquid or after it is obtained as a crude product. Alternatively, the compound obtained in each step can be isolated and/or purified from the reaction mixture by separation means such as concentration, crystallization, recrystallization, distillation, solvent extraction, fractionation, chromatography, or the like, according to the convention method.

- 15 [0129]

When the raw materials for each step and compounds of reagents are commercially available, commercially available products can be used as is.

[0130]

- 20 In the reaction of each step, reaction time may differ depending on the reagents or solvents used, but unless otherwise noted, it is normally 1 minute to 48 hours, preferably 10 minutes to 8 hours.

[0131]

- 25 In the reaction of each step, reaction temperature may differ depending on the reagents or solvents used, but unless otherwise noted, it is normally -78°C to 300°C, preferably -78°C to 150°C.

[0132]

In the reaction of each step, pressure may differ depending on the reagents or solvents used, but unless otherwise noted, it is normally 1 atm to 20 atm, preferably 1 atm to 3 atm.

[0133]

- 30 In the reaction of each step, for example, a microwave synthesis device such as Initiator made by Biotage may be used. Reaction temperature may differ depending on the reagents or solvents used, but unless otherwise noted, it is normally room temperature to 300°C, preferably 50°C to 250°C. Reaction time may differ depending on the reagents or solvents used, but unless otherwise noted, it is normally 1 minute to 48 hours, preferably 1 minute to 8 hours.

- 35 [0134]

In the reaction of each step, unless otherwise noted, a reagent is used in an amount of 0.5 equivalents to 20 equivalents with respect to mass, preferably 0.8 equivalents to 5 equivalents. When a reagent is used as a catalyst, the reagent is used in an amount of 0.001 equivalents to 1 equivalent with respect to mass, preferably 0.01 equivalents to 0.2 equivalents. When a reagent also serves as a reaction solvent, the reagent is used in the amount of solvent.

[0135]

In the reaction of each step, unless otherwise noted, these reactions are performed in the absence of a solvent or after dissolving or suspending in a suitable solvent. Specific examples of solvents include the solvents described in the examples or in the following:

- 10 alcohols: methanol, ethanol, tert-butyl alcohol, 2-methoxyethanol, and the like;
- ethers: diethyl ether, diphenyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and the like;
- aromatic hydrocarbons: chlorobenzene, toluene, xylene, and the like;
- saturated hydrocarbons: cyclohexane, hexane, and the like;
- amides: N,N-dimethylformamide, N-methylpyrrolidone, and the like;
- 15 halogenated hydrocarbons: dichloromethane, carbon tetrachloride, and the like;
- nitriles: acetonitrile, and the like;
- sulfoxides: dimethyl sulfoxide, and the like;
- aromatic organic bases: pyridine, and the like;
- anhydrides: acetic anhydride, and the like;
- 20 organic acids: formic acid, acetic acid, trifluoroacetic acid, and the like;
- inorganic acids: hydrochloric acid, sulfuric acid, and the like;
- esters: ethyl acetate, and the like;
- ketones: acetone, methyl ethyl ketone, and the like; and
- water.

- 25 The foregoing solvents may be used by mixing two or more kinds at appropriate ratios.

[0136]

When a base is used in the reaction of each process, for example, a base shown below or a base described in the examples may be used:

- inorganic bases: sodium hydroxide, magnesium hydroxide, sodium carbonate, calcium carbonate,
- 30 sodium bicarbonate, and the like;
- organic bases: triethylamine, diethylamine, pyridine, 4-dimethylaminopyridine, N,N-dimethylaniline, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene, imidazole, piperidine, and the like; metal alkoxides: sodium ethoxide, potassium tert-butoxide, and the like;
- alkali metal hydrides: sodium hydride, and the like;

metal amides: sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, and the like;
and

organolithium: m-butyl lithium and the like.

[0137]

5 When an acid or an acidic catalyst is used in the reaction of each process, for example, an acid or acidic catalyst shown below or an acid or acidic catalyst described in the examples may be used:

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

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

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

[0138]

15 The reaction of each step is, unless otherwise stated, performed according to a method known per se, for example, a method taught in: 5th Edition Experimental Chemistry Course, Volumes 13 to 19 (Compiled by The Chemical Society of Japan); New Experimental Chemistry Course, Volumes 14 and 15 (Compiled by the Chemical Society of Japan); Precision Organic Chemistry, Revised 2nd Edition (L. F. Tietze, Th. Eicher, Nankodo); Revised Organic Name
20 Reactions: Mechanisms and Important Points (by Hideo Togo, Kodansha); ORGANIC SYNTHESSES Collective Volumes I to VII (John Wiley & Sons Inc); Modern Organic Synthesis in the Laboratory A Collection of Standard Experiential Procedures (by Jie Jack Li, published by OXFORD UNIVERSITY); Comprehensive Heterocyclic Chemistry III, Vol. 1 to Vol. 14 (Elsevier Japan KK); Organic Synthesis Strategies Learned in Name Reactions (translated by Kiyoshi
25 Tomioka, published by Kagaku-Dojin); or Comprehensive Organic Transformations (VCH Publishers Inc.), published 1989; or the like; or a method described in the examples.

[0139]

 In each step, reactions to protect or deprotect a functional group are performed according to a method known per se, for example, a method taught in: "Protective Groups in Organic
30 Synthesis, 4th Ed.," published by Wiley-Interscience in 2007 (by Theodora W. Greene and Peter G. M. Wuts); "Protecting Groups 3rd Ed.," published by Thieme in 2004 (by P. J. Kocienski); or the like, or a method described in the examples.

 Examples of protecting groups for hydroxyl groups such as alcohols and phenolic hydroxyl groups include: ether protecting groups such as methoxymethyl ether, benzyl ether, tert-
35 butyldimethylsilyl ether, tetrahydropyranyl ether; carboxylate ester protecting groups such as

acetic acid esters; sulfonate ester protecting groups such as methanesulfonate esters; carbonate ester protecting groups such as tert-butyl carbonate.

Examples of protecting groups for aldehyde carbonyl groups include: acetal protecting groups such as dimethyl acetal; cyclic acetal protecting groups such as 1,3-dioxane; and the like.

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

10 Examples of protecting groups for carboxyl groups include: ester protecting groups such as methyl esters; amide protecting groups such as N,N-dimethylamide; and the like.

Examples of protecting groups for thiols include: ether protecting groups such as benzyl thioether; ester protecting groups such as thioacetate esters, thiocarbonates, and thiocarbamates; and the like.

15 Examples of protecting groups for amino groups and aromatic heterocycles such as imidazole, pyrrole, and indole include: carbamate protecting groups such as benzyl carbamate and tert-butyl carbamate; amide protecting groups such as acetamide; alkyl amine protecting groups such as N-triphenylmethylamine; sulfonamide protecting groups such as methanesulfonamide; 2-(trimethylsilyl)ethoxymethyl groups; and the like.

20 Removal of protecting groups can be performed using a method known per se, for example, a method using an acid, a base, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (for example, trimethylsilyl iodide, trimethylsilyl bromide), a reduction method, or the like.

[0140]

25 In each step, when performing a reduction reaction, examples of reducing agents used include: metal hydrides such as lithium aluminum hydride, sodium triacetoxyborohydride, sodium cyanoborohydride, diisobutylaluminum hydride (DIBAL-H), sodium borohydride, and tetramethylammonium triacetoxyborohydride; boranes such as borane tetrahydrofuran complex; Raney nickel; Raney cobalt; hydrogen; formic acid; triethylsilane; and the like. When reducing a carbon-carbon double bond or triple bond, there are methods for using a catalyst such as palladium-carbon or a Lindlar catalyst. Furthermore, when reducing a nitro group, there are methods such as using a catalyst such as rhodium-carbon in the presence of iron(II) acetate. Moreover, when
30 reducing an azide group, there are methods such as using triphenylphosphine in the presence of water.

[0141]

In each step, when performing an oxidation reaction, examples of oxidizing agents used include: peracids such as m-chloroperbenzoic acid (mCPBA), hydrogen peroxide, potassium peroxymonosulfate (OXONE®), and tert-butyl hydroperoxide; perchlorates such as tetrabutylammonium perchlorate; chlorates such as sodium chlorate; chlorites such as sodium chlorite; periodic acids such as sodium periodate; high valence iodine reagents such as iodosylbenzene; reagents containing manganese, such as manganese dioxide and potassium permanganate; lead compounds such as lead tetraacetate; reagents containing chromium, such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), and Jones reagents; halogen compounds such as N-bromosuccinimide (NBS); oxygen; ozone; sulfur trioxide-pyridine complexes; osmium tetroxide; selenium dioxide; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ); and the like.

[0142]

In each step, when performing a radical cyclization reaction, examples of radical initiators used include: azo compounds such as azobisisobutyronitrile (AIBN); water-soluble radical initiators such as 4-4'-azobis-4-cyanopentanoic acid (ACPA); triethylboron in the presence of air or oxygen; benzoyl peroxide; and the like. Furthermore, examples of radical reagents used include tributylstannane, tris(trimethylsilyl)silane, 1,1,2,2-tetraphenyldisilane, diphenylsilane, samarium iodide, and the like.

[0143]

In each step, when performing a Wittig reaction, examples of the Wittig reagent used include alkylidene phosphoranes and the like. Alkylidene phosphoranes can be prepared by methods known per se, for example, reacting a phosphonium salt with a strong base.

[0144]

In each step, when performing a Horner-Emmons reaction, examples of the reagents used include: phosphonoacetic esters such as methyl dimethylphosphonoacetate and ethyl diethylphosphonoacetate; bases such as an alkali metal hydrides or organolithium; and the like

[0145]

In each step, when performing a Friedel-Crafts reaction, examples of the reagents used include a combination of a Lewis acid and an acid chloride or a combination of a Lewis acid and an alkylating agent (for example, alkyl halides, alcohols, olefins, and the like). Alternatively, an organic acid or an inorganic acid can be used instead of a Lewis acid, and an acid anhydride such as acetic anhydride can be used instead of an acid chloride.

[0146]

In each step, when performing an aromatic nucleophilic substitution reaction, a nucleophilic agent (for example, phenols, amines, imidazole, and the like) and a base (for example, inorganic bases, organic bases, and the like) are used as the reagent.

[0147]

5 In each step, when performing a nucleophilic addition reaction using a carbanion, a nucleophilic 1,4-addition reaction using a carbanion (Michael addition reaction), or a nucleophilic substitution reaction using a carbanion, examples of bases used to generate carbanions include organolithium, metal alkoxides, inorganic bases, organic bases, and the like.

[0148]

10 In each step, when performing a Grignard reaction, examples of Grignard reagents used include arylmagnesium halides such as phenylmagnesium bromide; and alkylmagnesium halides such as methylmagnesium bromide. The Grignard reagent can be prepared by methods known per se, for example, reacting an alkyl halide or aryl halide with metal magnesium in the presence of an ether or tetrahydrofuran as a solvent.

15 [0149]

In each step, when performing a Knoevenagel condensation reaction, an active methylene compound (for example, malonic acid, diethyl malonate, malononitrile, or the like) and base (for example, organic bases, metal alkoxides, and inorganic bases) sandwiched between two electron attracting groups are used as reagents.

20 [0150]

In each step, when performing a Vilsmeier-Haack reaction, a combination of phosphoryl chloride and an amide derivative (for example, N, N-dimethylformamide or the like) or (chloromethylene)dimethyliminium chloride (Vilsmeier reagent) is used as a reagent.

[0151]

25 In each step, when performing an azidation reaction of alcohols, alkyl halides, or sulfonate esters, examples of azidation agents used include diphenylphosphoryl azide (DPPA), trimethylsilyl azide, sodium azide, and the like. For example, when azidizing alcohols, there are methods for using diphenylphosphoryl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), methods for using trimethylsilyl azide and a Lewis acid, and the like.

30 [0152]

In each step, when performing a reductive amination reaction, examples of reducers used include sodium triacetoxyborohydride, borane-2-methylpyridine complexes, sodium cyanoborohydride, hydrogen, formic acid, and the like. When the substrate is an amine compound, examples of carbonyl compounds used include not only paraformaldehyde but also aldehydes such as acetaldehyde and ketones such as cyclohexanone. When the substrate is a carbonyl compound,

35

examples of amines used include: primary amines such as ammonia and methylamine; and secondary amines such as dimethylamine.

[0153]

5 In each step, when performing a Mitsunobu reaction, azodicarboxylate esters (for example, diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and the like) and triphenylphosphine are used as reagents.

[0154]

10 In each step, when performing an esterification reaction, an amidation reaction, or a urea conversion reaction, examples of reagents used include: halogenated acyl bodies such as acid chlorides and acid bromides; and activated carboxylates such as acid anhydrides, active esters, and sulfate esters. When performing an amidation reaction using a non-activated ester, trimethylaluminum or the like is used as an activator. Examples of carboxylic acid activators include carbodiimide-based condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD); triazine-based condensing agents
15 such as 4-(4,6-dimethoxy-1,3,5-triazine-2-yl)-4-methylmorpholinium chloride-n-hydrate (DMT-MM); carbonate ester-based condensing agents such as 1,1-carbonyldiimidazole (CDI); diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-tris(dimethylamino)phosphonium salts (BOP reagents); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride; lower alkyl halides such as ethyl chloroformate; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-
20 tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; or a combination of these. When using a carbodiimide-based condensing agent, additives such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), and dimethylaminopyridine (DMAP) may be further added to the reaction.

[0155]

25 In each step, when performing a coupling reaction, examples of metal catalysts used include: palladium compounds such as palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), dichlorobis(triethylphosphine)palladium (II), tris(dibenzylideneacetone)dipalladium(0), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride; nickel compounds such as
30 tetrakis(triphenylphosphine)nickel(0); rhodium compounds such as tris(triphenylphosphine)rhodium(III) chloride; cobalt compounds; copper compounds such as copper oxide and copper(I) iodide; and platinum compounds. Additionally, a base may be added to the reaction, and examples of such bases include inorganic bases and the like.

[0156]

In each step, when performing a thiocarbonylation reaction, diphosphorus pentasulfide is typically used as the thiocarbonylation agent, but other than diphosphorus pentasulfide, reagents having 1,3,2,4-dithiadiphosphetane-2,4-disulfide structures such as 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) may be used.

5 [0157]

In each step, when performing a Wohl-Ziegler reaction, examples of halogenating agents used include N-iodosuccinimide, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), bromine, sulfuryl chloride, and the like. Additionally, by adding radical initiators such as heat, light, benzoyl peroxide, or azobisisobutyronitrile to the reaction, the reaction can be accelerated.

10 [0158]

In each step, when performing a halogenation reaction of a hydroxyl group, examples of halogenating agents used include acid halides of hydrohalogenic acids and inorganic acids, specifically, hydrochloric acid, thionyl chloride, phosphorus oxychloride, and the like when chlorinated and 48% hydrobromic acid and the like when brominated. Furthermore, methods for obtaining alkyl halides from alcohols may be used by the action between triphenylphosphine and carbon tetrachloride, carbon tetrabromide, or the like. Alternatively, a method for synthesizing an alkyl halide via a two-step reaction such as converting an alcohol into a sulfonate ester and then reacting with lithium bromide, lithium chloride, or sodium iodide may be used.

[0159]

20 In each step, when performing an Arbuzov reaction, examples of reagents used include: alkyl halides such as ethyl bromoacetate; and phosphites such as triethyl phosphite, tri(isopropyl) phosphite, and the like.

[0160]

In each step, when performing a sulfonate esterification reaction, examples of sulfonylating agents used include methanesulfonyl chloride, p-toluenesulfonyl chloride, methanesulfonate anhydride, trifluoromethanesulfonate anhydride, p-toluenesulfonate anhydride, and the like.

[0161]

In each step, when performing a hydrolysis reaction, an acid or base is used as a reagent. Furthermore, when performing an acid hydrolysis reaction of a tert-butyl ester, formic acid, triethylsilane, or the like may be added to reductively trap a tert-butyl cation, which is generated as a byproduct.

30 [0162]

In each step, when performing a dehydration reaction, examples of dehydrating agents used include sulfuric acid, diphosphorus pentoxide, phosphorus oxychloride, N,N'-dicyclohexylcarbodiimide, alumina, polyphosphoric acid, and the like.

[0163]

In each step, when performing an alkylation reaction, bases used include potassium carbonate, tripotassium phosphate, triethylamine, N,N-diisopropylethylamine, pyridine, sodium ethoxide, potassium tert-butoxide, sodium hydride, lithium hexamethyldisilazide, sodium
5 hexamethyldisilazide, n-butyllithium, and the like.

[0164]

In each step, when performing an aromatic electrophilic substitution reaction, an electrophilic agent (for example, a halogenating agent, a nitrating agent, or the like) is used as a reagent. Examples of halogenating agents used include N-iodosuccinimide, N-bromosuccinimide
10 (NBS), N-chlorosuccinimide (NCS), bromine, bis(tetrafluoroborate)1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane (SelectFluor®), and the like. Furthermore, examples of nitrating agents used include nitric acid and the like.

[0165]

In each step, when performing a Leimgruber-Batcho indole synthesis reaction, a carbon
15 chain homologation agent (for example, N,N-dimethylformamide dimethyl acetal or the like) and a reducing agent (for example, a hydrogen atmosphere, catalytic amounts of iron (II) acetate, and rhodium-carbon, or the like) are used as reagents.

[0166]

In each step, when performing a deoxyfluorination reaction, examples of fluorinating
20 agents include bis(2-methoxyethyl)aminosulfur trifluoride, diethylaminosulfur trifluoride, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, N,N-diethyl-S,S-difluorophenylsulfyliminium tetrafluoroborate, difluoro-4-morpholinylsulfonium tetrafluoroborate, and the like.

[0167]

In each step, when performing a decarboxylative fluorination reaction,
25 bis(tetrafluoroborate)1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane (SelectFluor®) and an inorganic base (for example, lithium carbonate, lithium acetate, potassium fluoride, or the like) are used.

[0168]

Compound (I) can be synthesized according to a method exemplified in production
30 methods A to H described below or by methods corresponding thereto.

Unless specifically described otherwise, symbols in each general formula in the reaction formulae each have the same meaning as above. In the formulae, R^a represents a C₁₋₃ alkyl group that may be substituted. Examples of C₁₋₃ alkyl groups that may be substituted include C₁₋₃ alkyl groups which may have one to three substituents selected from the substituent group A. Among
35 these, C₁₋₃ alkyl groups (for example, a methyl group) are preferable. X represents a halogen atom

(for example, a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom). P¹ represents a protecting group (for example, tert-butyldimethylsilyl ether) of an alcoholic hydroxyl group. P² represents a protecting group (for example, benzyl ether) of a phenolic hydroxyl group.

[0169]

- 5 Note, raw material compounds used in each production method are either commercially available or can be produced by methods known per se.

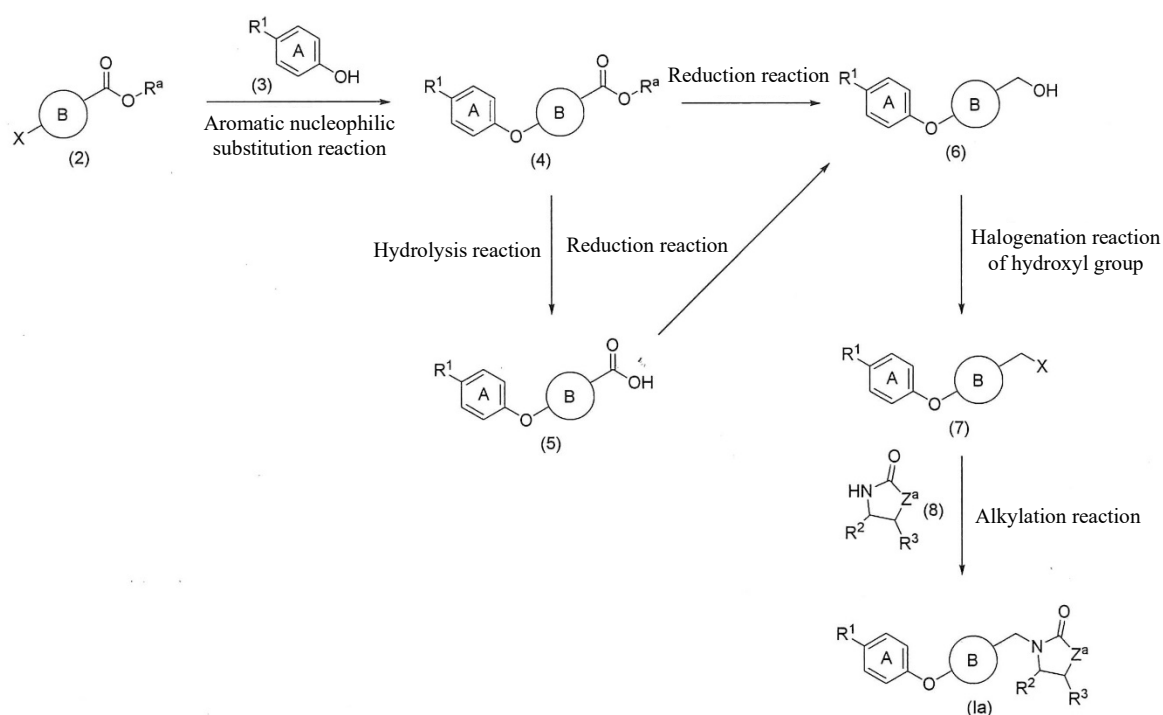
[0170]

Compound (Ia), wherein Z is CH₂, CF₂, or O in compound (I), can be produced from compound (2) by the following method.

- 10 [Production Method A]

[0171]

[Chemical Formula 15]



[0172]

- 15 (In the formula, Z^a is CH₂, CF₂, or O, and all other symbols have the same meaning as above.)

[0173]

- 20 Compound (4) can be produced by subjecting compound (2) to an aromatic nucleophilic substitution reaction together with compound (3). Potassium carbonate or the like can be used as the base. Compound (6) can be produced by subjecting compound (4) to a reduction reaction. Furthermore, compound (6) can be produced by subjecting compound (5) obtained by hydrolyzing compound (4) to a reduction reaction. Compound (7) can be produced by halogenating a hydroxyl

group of compound (6). Examples of reagents used include phosphorus tribromide and the like. Compound (Ia) can be produced by subjecting compound (7) to an alkylation reaction together with compound (8).

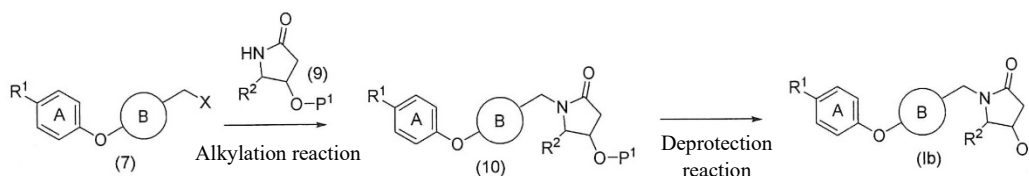
[0174]

- 5 Compound (Ib), wherein Z^a is CH_2 and R^3 is a hydroxyl group in compound (Ia), can be produced from compound (7) by the following method.

[Production Method B]

[0175]

[Chemical Formula 16]



10

[0176]

Compound (Ib) can also be produced by deprotecting compound (10) obtained by subjecting compound (7) to an alkylation reaction together with compound (9).

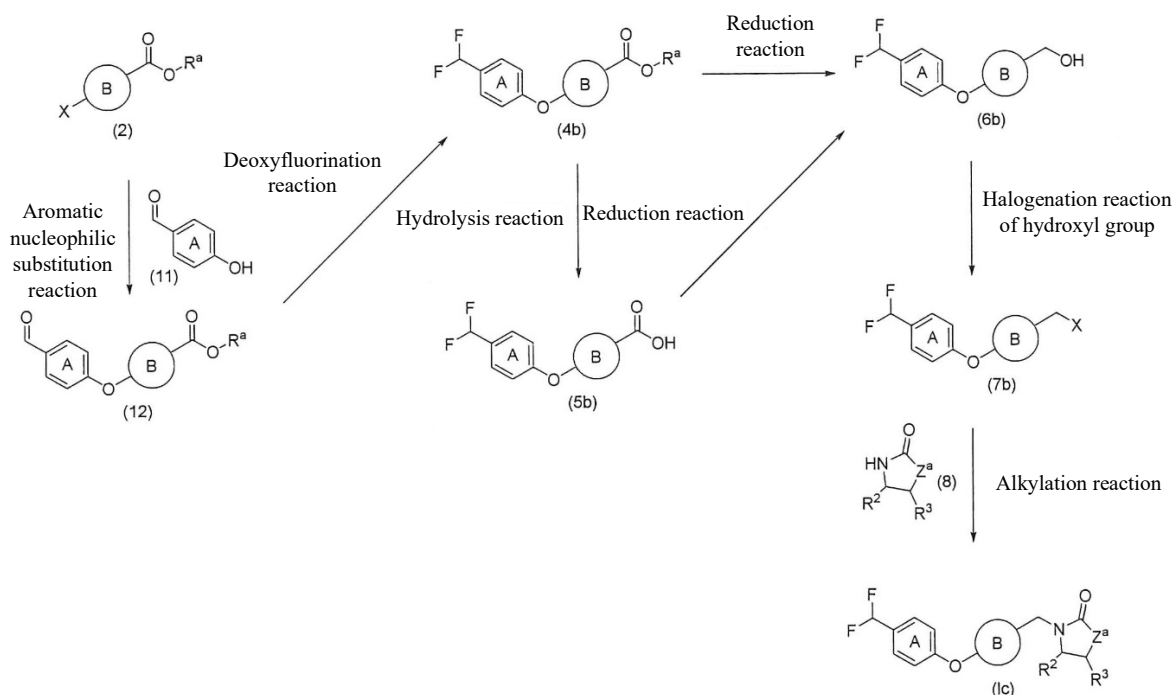
[0177]

- 15 Compound (Ic), wherein R^1 is a difluoromethyl group in compound (Ia), can also be produced from compound (2) by the following method.

[Production Method C]

[0178]

[Chemical Formula 17]



[0179]

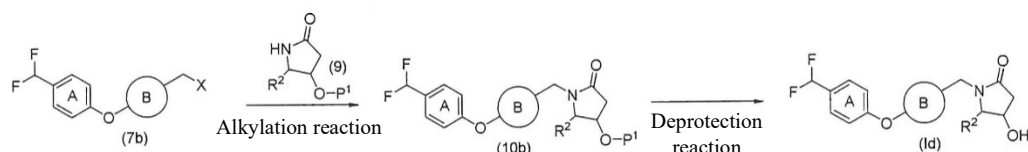
Compound (12) can be produced by subjecting compound (2) to an aromatic nucleophilic substitution reaction together with compound (11). Compound (4b) can be produced by subjecting compound (12) to a deoxidation fluorination reaction. Compound (6b) can be produced by subjecting compound (4b) to a reduction reaction. Furthermore, compound (6b) can be produced by subjecting compound (5b) obtained by hydrolyzing compound (4b) to a reduction reaction. Compound (7b) can be produced by halogenating a hydroxyl group of compound (6b). Compound (1c) can be produced by subjecting compound (7b) to an alkylation reaction together with compound (8).

[0180] Compound (1d), wherein Z^a is CH_2 and R^3 is a hydroxyl group in compound (1c), can also be produced from compound (7b) by the following method.

[Production Method D]

[0181]

[Chemical Formula 18]



[0182]

Compound (1d) can be produced by deprotecting compound (10b) obtained by subjecting compound (7b) to an alkylation reaction together with compound (9).

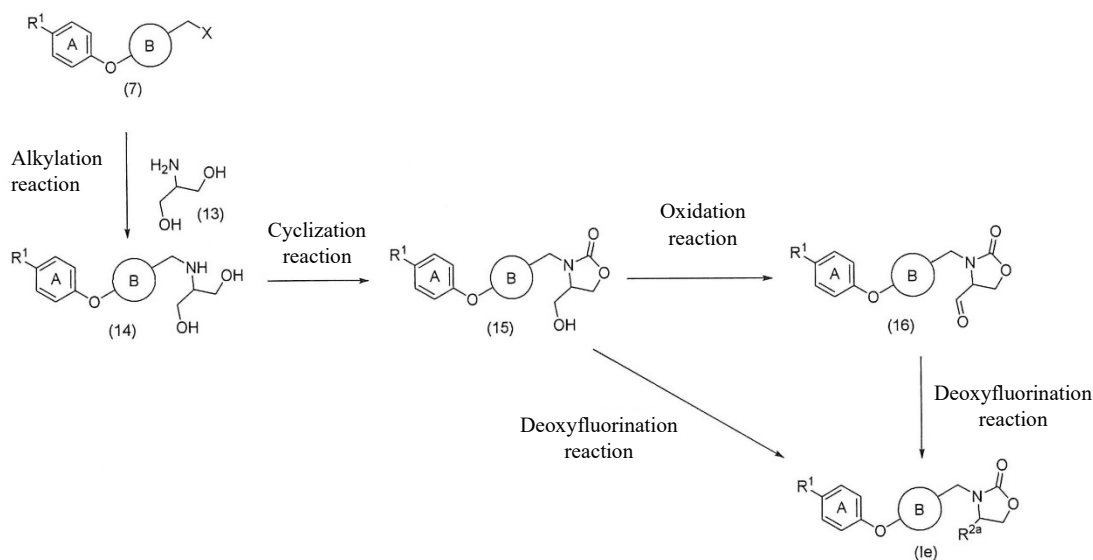
[0183]

Compound (Ie), wherein Z^a is O and R^2 is a monofluoromethyl group or a difluoromethyl group in compound (Ia), can also be produced from compound (7b) by the following method.

[Production Method E]

[0184]

5 [Chemical Formula 19]



[0185]

(In the formula, R^{2a} is a monofluoromethyl group or a difluoromethyl group, and all other symbols have the same meaning as above.)

10 [0186]

Compound (14) can be produced by subjecting compound (7) to an alkylation reaction together with compound (13). Compound (15) can be produced by subjecting compound (14) to a cyclization reaction in the presence of a base. Examples of cyclization agents used include triphosgene and the like, and examples of bases include triethylamine and the like. Compound (Ie) can be produced by subjecting compound (15) to a deoxyfluorination reaction. Furthermore, compound (Ie) can be produced by subjecting compound (16) obtained by hydrolyzing compound (15) to a deoxyfluorination reaction.

[0187]

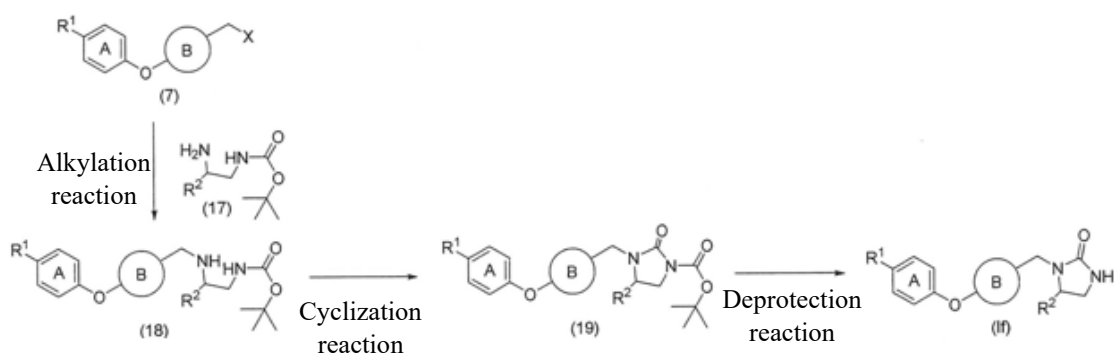
20 Compound (If), wherein Z is NH and R^3 is a hydrogen atom in compound (I), can also be produced from compound (7) by the following method.

[Production Method F]

[0188]

[Chemical Formula 20]

5



[0189]

10 Compound (18) can be produced by subjecting compound (7) to an alkylation reaction together with compound (17). Compound (19) can be produced by subjecting compound (18) to a cyclization reaction in the presence of a base. Examples of cyclization agents include triphosgene and the like, and examples of bases include triethylamine and the like. Compound (If) can be produced by deprotecting compound (19).

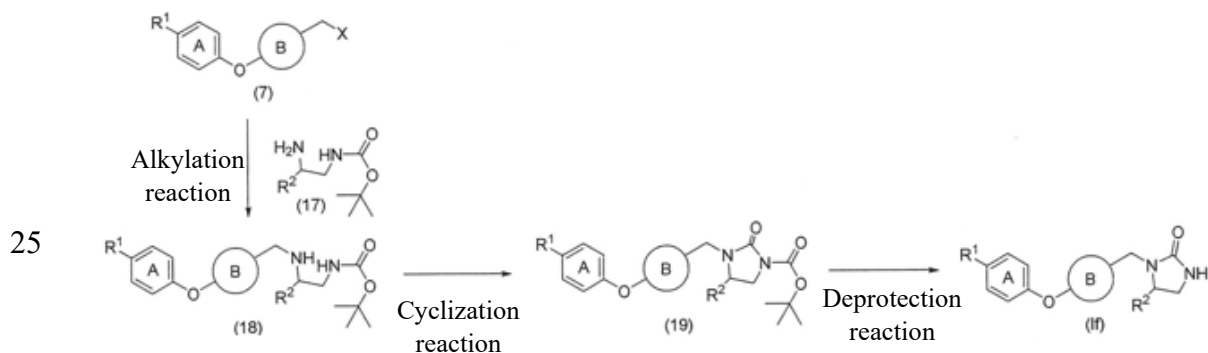
15 [0190]

Compound (Ia), wherein Z is CH₂, CF₂, or O in compound (I), can also be produced from compound (20) by the following method.

[Production Method G]

[0191]

20 [Chemical Formula 21]



25

[0192]

30 Compound (21) can be produced by subjecting compound (20) to an alkylation reaction together with compound (8). Compound (22) can be obtained by deprotecting compound (21). Compound (Ia) can be produced by coupling compound (22) with compound (23).

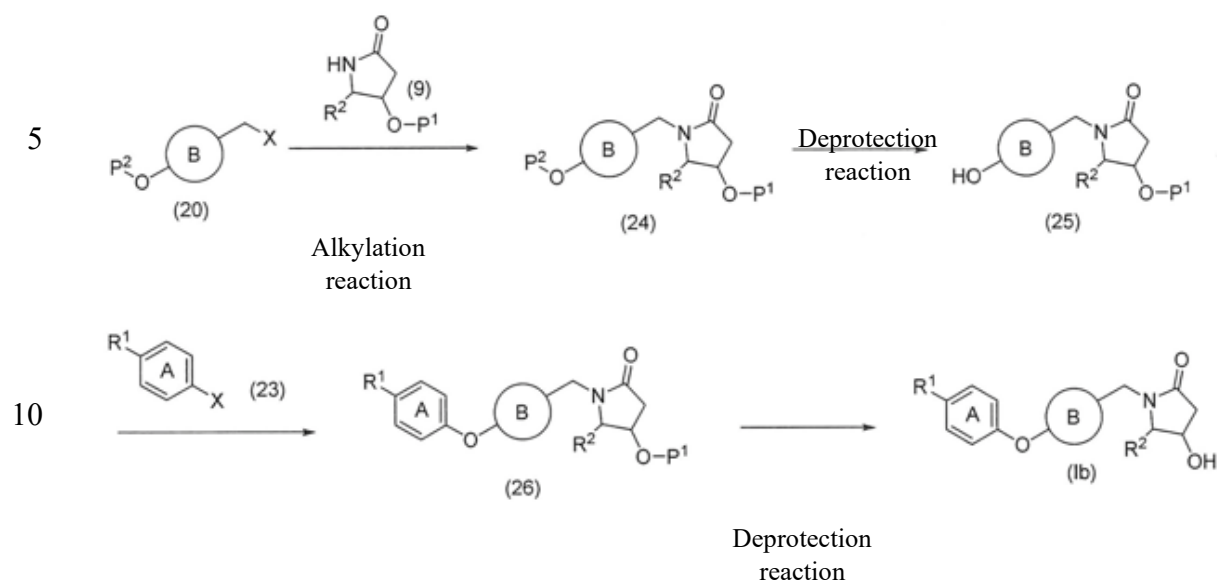
[0193]

Compound (Ib), wherein Z^a is CH₂ and R³ is a hydroxyl group in compound (Ia), can also be produced from compound (20) by the following method.

35 [Production Method H]

[0194]

[Chemical Formula 22]



[0195]

Compound (24) can be produced by subjecting compound (20) to an alkylation reaction together with compound (9). Compound (25) can be produced by deprotecting the P² group of compound (24). Compound (Ib) can be produced by deprotecting the P¹ group of compound (26) obtained by coupling compound (25) with compound (23).

[0196]

The intramolecular functional group in compound (I) obtained by such can also be converted to a target functional group by combining chemical reactions known per se. Here, examples of chemical reactions include oxidation reactions, reduction reactions, alkylation reactions, acylation reactions, urea addition reactions, hydrolysis reactions, amination reactions, esterification reactions, aryl coupling reactions, deprotecting reactions, and the like.

[0197]

Compound (I) obtained by the above production method can be isolated and purified by known procedures, for example, solvent extraction, pH conversion of solution, dissolution, crystallization, recrystallization, and chromatography.

[0198]

When compound (I) includes an optical isomer, stereoisomer, positional isomer, or rotational isomer, these are also included as compound (I) and each can be obtained individually by synthesis

methods and separation methods known per se. For example, when compound (I) has an optical isomer, optical isomers resolved from the compound are also included in compound (I).

At this point, optical isomers can be produced by methods known per se.

[0199]

5 Compound (I) may be a crystal.

A crystal of compound (I) (abbreviated as crystal of the present invention below) applies a crystallization method known per se to compound (I) to enable production by crystallization.

The crystal of the present invention has excellent physiochemical properties (for example, melting point, solubility, and stability) and biological properties (for example, pharmacokinetics
10 (absorption, distribution, metabolism, and excretion) and medicinal effects) and is expected to be useful as a medicine.

[Examples]

[0200]

The present invention is described in further detail using the following examples, test examples,
15 and production examples. These do not limit the present invention and may be changed so long as they do not deviate from the scope of the present invention.

“Room temperature” in the following examples indicates a normal temperature of about 10° to about 35°. In mixed solvents, the indicated ratio indicates a volumetric ratio unless specifically noted otherwise. % indicates the weight % unless specifically noted otherwise. Elution of the
20 examples in column chromatography was performed under observation using TLC (thin layer chromatography, thin layer chromatography). A 60 F₂₅₄ made by Merck (Merck) was used as a TLC plate for TLC observation, and a solvent used as an elution solvent in column chromatography was used as a developing solvent. Further, a UV detector was employed for detection. In silica gel column chromatography, when NH is stated, aminopropylsilane-bound silica gel was used, and
25 when Diol is stated, 3-(2,3-dihydroxypropoxy)propylsilane-bound silica gel was used. In preparative HPLC (high-performance liquid chromatography), when C18 is stated, octadecyl-bound silica gel was used. The ratio indicated in elution solvents indicates a capacity ratio unless stated specifically otherwise.

ACD/SpecManager (product name) software or the like was used in ¹H NMR analysis. Extremely
30 gradual proton peaks such as those of hydroxyl groups or amino groups are not described hereinafter.

MS was measured by LC/MS. An ESI method or APCI method was used as an ionization method. Data indicate measured values (found). Molecular ion peaks are commonly observed and are sometimes observed as fragment ions. For salts, free molecular ion peaks or fragment ion peaks
35 are commonly observed.

The unit of sample concentration (c) for optical rotation ($[\alpha]_D$) is g/100 mL.

The elemental analysis value (anal.) is indicated as a calculated value (calcd) and a measured value (found).

5 Peak according to powder x-ray diffraction of the examples mean peaks measured at room temperature using an Ultima IV (Rigaku Corporation, Japan) using the CuK α line as a baseline.

The measurement conditions are as follows.

Electric pressure/electric current : 40 kV/50 mA

Scan speed: 6 degrees/min

Scan range of 2 theta: 2 to 35 degrees

10 The degree of crystallization according to powder x-ray diffraction of the examples is calculated by the Hermans method.

[0201]

The abbreviations below are used in the following examples.

mp: melting point

15 MS: mass spectrum

M: molar concentration

N: normality

CDCl₃: heavy chloroform

DMSO-d₆: heavy dimethyl sulfoxide

20 ¹H NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatograph mass spectrometer

ESI: electrospray ionization, electrospray ionization

APCI: atmospheric pressure chemical ionization, atmospheric pressure chemical ionization

IPE: diisopropyl ether

25 DMF: N,N-dimethylformamide

THF: tetrahydrofuran

MeOH: methanol

MeCN: acetonitrile

NMP: N-methylpyrrolidone

30 [0202]

Example 13

(4S,5S)-4-hydroxy-5-methyl-1- $\{[6-(4\text{-methylphenoxy})\text{pyridine-3-yl}]\text{methyl}\}$
pyrrolidine-2-one

A) Methyl 6-(p-tolyloxy)nicotinate

Potassium carbonate (8.55 g) was added at room temperature to a DMF (80 mL) suspension of methyl 6-fluoronicotinate (8.00 g) and p-cresol (5.96 mL), and the mixture was stirred for three hours at 80°C. After diluting with water, the resulting precipitate was filtered and washed with water to obtain the compound of the heading (12.5 g).

5 MS: $[M+H]^+$ 244.1.

[0203]

B) (6-(p-Tolyloxy)pyridine-3-yl)methanol

Sodium borohydride (6.61 g) was added at room temperature to a THF (100 mL) / MeOH (20 mL) suspension of methyl 6-(p-tolyloxy)nicotinate (11.5 g) and stirred overnight. Then, the
10 mixture was stirred for three hours at 60°C. After diluting with an aqueous ammonium chloride solution and ethyl acetate, the mixture was extracted using ethyl acetate. After washing with a saturated saline solution, the organic layer was dried using sodium sulfate and concentrated under reduced pressure. The residue was powderized using hexane to obtain the compound of the heading (9.46 g).

15 MS: $[M+H]^+$ 216.1.

[0204]

C) 5-(Bromomethyl)-2-(p-tolyloxy)pyridine

Phosphorus tribromide (0.389 mL) was added at 0°C to a mixture of (6-(p-tolyloxy)pyridine-3-yl)methanol (740 mg) and THF (10 mL)

20 and stirred for three hours at room temperature.

After diluting with ethyl acetate and water, the mixture was extracted using ethyl acetate. After washing with an aqueous sodium hydrogen carbonate solution and a saturated saline solution, the organic layer was dried using sodium sulfate and concentrated under reduced pressure. The residue was powderized using hexane/

25 ethyl acetate to obtain the compound of the heading (842 mg).

MS: $[M+H]^+$ 278.0.

[0205]

D) (4S,5S)-4-Hydroxy-5-methyl-1- $\{[6-(4\text{-methylphenoxy})\text{pyridine-3-yl}]\text{methyl}\}$ pyrrolidine-2-one

30 A 0.5 M potassium hexamethyldisilazide toluene solution (19.2 mL) was added at 0°C to a mixture of (4s,5s)-4-((tert-butyldimethylsilyl)oxy)-5-methylpyrrolidine-2-one (2.00 g), 5-(bromomethyl)-2-(p-tolyloxy)pyridine (3.64 g), and THF (20 mL) and stirred overnight at room temperature.

After diluting with ethyl acetate and water, the mixture was extracted using ethyl acetate. After
35 washing with a saturated saline solution, the organic layer was dried using sodium sulfate and

concentrated under reduced pressure. The residue was purified using silica gel column chromatography (NH, ethyl acetate/hexane) to obtain (4S,5S)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-1-((6-(p-tolyloxy)pyridine-3-yl)methyl)pyrrolidine-2-one (2.13 g). This was dissolved in THF (10 mL), a 4M hydrogen chloride cyclopentyl methyl ether solution (20 mL) was added at room temperature, and the mixture was stirred for three hours at 60°C.

After diluting with ethyl acetate and an aqueous saturated sodium bicarbonate solution, the mixture was extracted using ethyl acetate. After washing with a saturated saline solution, the organic layer was dried using sodium sulfate and concentrated under reduced pressure. The residue was purified using silica gel column chromatography (NH, ethyl acetate/hexane, and ethylacetate/methanol) and powderized using hexane/ethylacetate to obtain the compound of the heading (1.24 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (3H, d, J = 6.8 Hz), 2.15 (1H, dd, J = 16.6, 3.4 Hz), 2.31 (3H, s), 2.52-2.61 (1H, m), 3.43-3.55 (1H, m), 4.07 (1H, d, J = 15.4 Hz), 4.11-4.21 (1H, m), 4.59 (1H, d, J = 15.4 Hz), 5.06 (1H, d, J = 4.9 Hz), 6.90-7.02 (3H, m), 7.20 (2H, d, J = 7.9 Hz), 7.66 (1H, dd, J = 8.5, 2.4 Hz), 8.01 (1H, d, J = 1.9 Hz).

[0206]

Example 37

Methyl (4S,5S)-1-{{6-(2,4-difluorophenoxy)pyridine-3-yl}methyl}-4-hydroxy-5-methylpyrrolidine-2-one

A) Methyl 6-(2,4-difluorophenoxy)nicotinate

A mixture of methyl 6-fluoronicotinate (4.31 g), 2,4-difluorophenol (3.80 g), potassium carbonate (5.76 g), and MeCN (30 mL) was stirred for 16 hours at 60°C. The mixture was diluted with ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using a 10% aqueous potassium carbonate solution and a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure to obtain the compound of the heading (7.37 g).

MS: [M+H]⁺ 266.3.

[0207]

B) Methyl (6-(2,4-difluorophenoxy)pyridine-3-yl)methanol

Sodium borohydride (4.21 g) was added at room temperature to a THF (60 mL) / MeOH (15 mL) suspension of methyl 6-(2,4-difluorophenoxy)nicotinate (7.37 g), and the mixture was stirred for three hours at 60°C.

Sodium borohydride (4.21 g) was added at room temperature, and the mixture was stirred for an additional three hours at 60°C. The solvent was distilled off, and the mixture was diluted with

water and extracted using ethyl acetate. The organic layer was washed using a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure to obtain the compound of the heading (6.59 g).

MS: $[M+H]^+$ 238.3.

5 [0208]

C) 5-(Bromomethyl)-2-(2,4-difluorophenoxy)pyridine

Phosphorus tribromide (2.90 mL) was added at 0°C to a mixture of (6-(2,4-difluorophenoxy)pyridine-3-yl)methanol (6.59 g) and THF (70 mL) and stirred for 16 hours at room temperature.

10 The mixture was diluted using ethyl acetate, and this solution was washed using an aqueous sodium hydrogen carbonate solution and a saturated saline solution and dried using sodium sulfate. The residue was purified using silica-gel column chromatography (ethyl acetate/hexane) to obtain the compound of the heading (7.07 g).

^1H NMR (300 MHz, DMSO- d_6) δ 4.72 (2H, s), 7.10-7.20 (2H, m), 7.36-7.50 (2H, m),

15 7.96 (1H, dd, $J = 8.5, 2.4$ Hz), 8.18 (1H, d, $J = 2.3$ Hz).

[0209]

D) (4S,5S)-4-((tert-Butyldimethylsilyl)oxy)-1-((6-(2,4-difluorophenoxy)pyridin-3-yl)methyl)-5-methylpyrrolidine-2-one

20 A 1.6 M butyllithium hexane solution (6.16 mL) was added at -78°C to a mixture of (4S,5S)-4-((tert-butyldimethylsilyl)oxy)-5-methylpyrrolidine-2-one (2.26 g) and THF (40 mL) and stirred for 30 minutes at 0°C. 5-(bromomethyl)-2-(2,4-difluorophenoxy)pyridine (2.96 g) was added to the mixture and stirred for 1 hour at room temperature then stirred for an additional 7.5 hours at 50°C. After diluting with ethyl acetate and water, the mixture was extracted using ethyl acetate. The organic layer was washed using a saturated saline solution, dried using sodium sulfate, passed
25 through an NH silica gel pad, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (ethyl acetate/hexane) to obtain the compound of the heading (2.30 g).

MS: $[M+H]^+$ 449.2.

[0210]

30 E) (4S,5S)-1-{(6-(2,4-Difluorophenoxy)pyridine-3-yl)methyl}-4-hydroxy-5-methylpyrrolidine-2-one

A mixture of (4S,5S)-4-((tert-butyldimethylsilyl)oxy)-1-((6-(2,4-difluorophenoxy)pyridine-3-yl)methyl)-5-methylpyrrolidine-2-one (2.29 g) and a 2M hydrogen chloride ethanol solution (40 mL) were stirred for one hour at room temperature.

After concentration, the residue was diluted using aqueous sodium hydrogen carbonate solution, then extracted using ethyl acetate. After washing with a saturated saline solution, the organic layer was dried using sodium sulfate and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate/hexane and ethyl acetate/methanol) to obtain a crude product. This was dissolved at 80°C in ethyl acetate, heptane was added dropwise to the solution, and the resulting suspension was stirred for 18 hours at room temperature.

The precipitate was filtered out and dried under reduced pressure at 60°C to obtain the compound of the heading (1.47 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (3H, d, J = 6.8 Hz), 2.14 (1H, dd, J = 16.6, 3.0 Hz), 2.52-2.63 (1H, m), 3.44-3.54 (1H, m), 4.04-4.21 (2H, m), 4.59 (1H, d, J = 15.4 Hz), 5.05 (1H, d, J = 4.9 Hz), 7.06-7.19 (2H, m), 7.32-7.48 (2H, m), 7.71 (1H, dd, J = 8.5, 2.4 Hz), 7.97 (1H, d, J = 1.9 Hz). [0211]

Example 38

(4S,5S)-1-({6-[4-(Difluoromethyl)-2-fluorophenoxy]pyridine-3-yl}methyl)-4-hydroxy-5-methylpyrrolidine-2-one

A) Methyl 6-(2-fluoro-4-formylphenoxy)nicotinate

A mixture of methyl 6-fluoronicotinate (12.2 g), 3-fluoro-4-hydroxybenzaldehyde (11.0 g), potassium carbonate (16.3 g), and NMP (75 mL) was stirred for 16 hours at 90°C.

The mixture was diluted with ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using a 10% aqueous potassium carbonate solution and a saturated saline solution, dried using sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate/hexane) and crystallized using hexane to obtain the compound of the heading (17.4 g).

MS: [M+H]⁺ 276.0.

[0212]

B) Methyl 6-(4-(Difluoromethyl)-2-fluorophenoxy)nicotinate

(Diethylamino)sulfur trifluoride (11.5 mL) was added to a toluene (90 mL) solution of methyl 6-(2-fluoro-4-formylphenoxy)nicotinate (8.00 g) at 0°C, and the mixture was stirred for one day at room temperature. After adding MeOH (10 mL) to stop the reaction, the mixture was diluted using a 10% potassium carbonate aqueous solution and extracted using ethyl acetate. The organic layer was washed using a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (8.14 g) was obtained.

MS: [M+H]⁺ 298.0.

[0213]

C) (6-(4-(Difluoromethyl)-2-fluorophenoxy)pyridine-3-yl)methanol

Sodium borohydride (4.14 g) was added to a THF (60 mL) / MeOH (15 mL) suspension of methyl 6-(4-(difluoromethyl)-2-fluorophenoxy)nicotinate (8.14 g) at room temperature, and the mixture was stirred for 1 hour at 60°C. Sodium borohydride (4.14 g) was added at room temperature, and the mixture was stirred for an additional hour at 60°C. The mixture was diluted using water and extracted using ethyl acetate. The organic layer was washed using a saturated saline solution, dried using sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (5.33 g) was obtained.

MS: $[M+H]^+$ 270.0.

[0214]

D) 5-(Bromomethyl)-2-(4-(difluoromethyl)-2-fluorophenoxy)pyridine

Phosphorus tribromide (0.357 mL) was added to a mixture of (6-(4-difluoromethyl)-2-fluorophenoxy)pyridine-3-yl)methanol (920 mg) and THF (10 mL) at 0°C, and this was stirred for 16 hours at room temperature. After diluting the mixture using ethyl acetate, the solution was washed using a sodium hydrogen carbonate aqueous solution and a saturated saline solution and dried using sodium sulfate. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (977 mg) was obtained.

MS: $[M+H]^+$ 332.0.

[0215]

E) (4S,5S)-4-((tert-Butyldimethylsilyl)oxy)-1-((6-(4-(difluoromethyl)-2-fluorophenoxy)pyridine-3-yl)methyl)-5-methylpyrrolidine-2-one

A 1.6 M butyllithium hexane solution (4.50 mL) was added to a mixture of (4S,5S)-4-((tert-butyldimethylsilyl)oxy)-5-methylpyrrolidine-2-one (1.65 g) and THF (24 mL) at -78°C, and this was stirred for 30 minutes at 0°C. 5-(Bromomethyl)-2-(4-(difluoromethyl)-2-fluorophenoxy)pyridine (2.39 g) was added to the mixture, and this was stirred for 20 minutes at room temperature. Afterward, this was stirred for 22 hours at 50°C and stirred for 48 hours at 40°C. The mixture was diluted using ethyl acetate and water and afterward extracted using ethyl acetate. The organic layer was washed using a saturated saline solution. Afterward, this was dried using sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (2.15 g) was obtained.

MS: $[M+H]^+$ 481.2.

[0216]

F) (4S,5S)-1-(6-[4-(difluoromethyl)-2-fluorophenoxy]pyridine-3-yl)methyl-4-hydroxy-5-methylpyrrolidine-2-one

A mixture of (4S,5S)-4-((tert-butyldimethylsilyl)oxy)-1-((6-(4-(difluoromethyl)-2-fluorophenoxy)pyridine-3-yl)methyl)-5-methylpyrrolidine-2-one (2.14 g) and a 2 M hydrogen chloride ethanol solution (40 mL) was stirred for 18 hours at room temperature. After this was concentrated, the residue was diluted using a sodium hydrogen carbonate aqueous solution. Afterward, this was extracted using ethyl acetate. The organic layer was washed using a saturated saline solution. Afterward, this was dried using sodium sulfate and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane and ethyl acetate / methanol), and a crude product (1.61 g) was obtained. This was dissolved in warmed ethyl acetate (5 mL), heptane (8 mL) was dripped into this solution at room temperature, and the mixture was stirred for 15 minutes. Heptane (16 mL) was dripped into the obtained mixture at room temperature, and the mixture was stirred for an additional 30 minutes. Heptane (16 mL) was dripped into the obtained mixture at room temperature, and the mixture was stirred for an additional 72 hours. The precipitate was filtered out and dried under reduced pressure, whereupon the compound of the heading (1.52 g) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (3H, d, J = 6.8 Hz), 2.15 (1H, dd, J = 16.6, 3.4 Hz), 2.52-2.61 (1H, m), 3.45-3.55 (1H, m), 4.06-4.21 (2H, m), 4.59 (1H, d, J = 15.4 Hz), 5.07 (1H, d, J = 4.9 Hz), 7.07 (1H, t, J = 57.0 Hz), 7.15 (1H, d, J = 8.7 Hz), 7.47 (2H, d, J = 4.1 Hz), 7.61 (1H, d, J = 10.9 Hz), 7.74 (1H, dd, J = 8.5, 2.4 Hz), 7.99 (1H, d, J = 1.9 Hz).

[0217]

Example 45

(5S)-1-{[2-(2,4-Difluorophenoxy)pyrimidine-5-yl]methyl}-5-methylpyrrolidine-2-one

A) Methyl 2-(2,4-Difluorophenoxy)pyrimidine-5-carboxylate

A mixture of methyl 2-chloropyrimidine-5-carboxylate (5.00 g), 2,4-difluorophenol (2.77 mL), potassium carbonate (6.01 g), and MeCN (60 mL) was stirred for 16 hours at room temperature. The mixture was diluted using ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using a 10% potassium carbonate aqueous solution and a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure. The residue was crystallized using hexane, whereupon the compound of the heading (7.18 g) was obtained.

MS: [M+H]⁺267.0.

[0218]

B) 2-(2,4-Difluorophenoxy)pyrimidine-5-carboxylic acid

A 2 M sodium hydroxide aqueous solution (20.2 mL) was added to a mixture of methyl 2-(2,4-difluorophenoxy)pyrimidine-5-carboxylate (7.18 g) and THF (80 mL) at room temperature, and the mixture was stirred for 5 hours. After concentrating the reaction mixture under reduced pressure, this was diluted using water (40 mL) and neutralized using 1 M hydrochloric acid (40 mL). The obtained precipitate was filtered out and washed using water, whereupon the compound of the heading (4.98 g) was obtained.

MS: $[M-H]^+$ 250.9.

[0219]

C) (2-(2,4-Difluorophenoxy)pyrimidine-5-yl)methanol

Isobutyl chloroformate (3.07 mL) and 4-methylmorpholine (3.25 mL) were added to a mixture of 2-(2,4-difluorophenoxy)pyrimidine-5-carboxylic acid (4.97 g) and THF (80 mL)

at 0°C, and the mixture was stirred for 1 hour at the same temperature. Sodium borohydride (1.86 g) and water (20 mL) were dripped therein at 0°C, and the mixture was stirred for an additional 16 hours at room temperature. The mixture was diluted using ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using a 10% potassium carbonate aqueous solution and a saturated saline solution, dried using sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (2.93 g) was obtained.

^1H NMR (300 MHz, DMSO- d_6) δ 4.50 (2H, d, $J = 5.7$ Hz), 5.38 (1H, t, $J = 5.7$ Hz), 7.11-7.21 (1H, m), 7.41-7.53 (2H, m), 8.59 (2H, s).

[0220]

D) 5-(Bromomethyl)-2-(2,4-difluorophenoxy)pyrimidine

Phosphorus tribromide (1.29 mL) was added to a mixture of (2-(2,4-difluorophenoxy)pyrimidine-5-yl)methanol (2.93 g) and THF (30 mL) at 0°C, and this was stirred for 16 hours at room temperature. The mixture was diluted using ethyl acetate, and the solution was washed using a sodium hydrogen carbonate aqueous solution and a saturated saline solution and dried using sodium sulfate. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane), whereupon the compound of the heading (2.34 g) was obtained.

MS: $[M+H]^+$ 300.9.

[0221]

E) (5S)-1- {[2-(2,4-Difluorophenoxy)pyrimidine-5-yl]methyl} -5-methylpyrrolidine-2-one

A 1.6 M butyllithium hexane solution (2.30 mL) was added to a mixture of (S)-5-methylpyrrolidine-2-one (0.364 g) and THF (12 mL) at -78°C, and this was stirred for 30 minutes at 0°C. 5-(Bromomethyl)-2-(2,4-difluorophenoxy)pyrimidine (1.11 g) was added to the mixture,

and this was stirred for 1.5 hours at room temperature. The mixture was diluted using ethyl acetate and an ammonium chloride aqueous solution and afterward extracted using ethyl acetate. After washing the organic layer using a saturated saline solution, this was dried using sodium sulfate, passed through a silica gel / NH silica gel pad, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (NH, ethyl acetate / hexane) and recrystallized using ethyl acetate / heptane, whereupon the compound of the heading (0.621 g) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.13 (3H, d, J = 6.4 Hz), 1.44-1.59 (1H, m), 2.06-2.34 (3H, m), 3.52-3.64 (1H, m), 4.17 (1H, d, J = 15.8 Hz), 4.56 (1H, d, J = 15.4 Hz), 7.11-7.21 (1H, m), 7.41-7.53 (2H, m), 8.55 (2H, s).

[0222]

Example 49

(4S)-3-{[2-(4-Chloro-2-fluorophenoxy)pyrimidine-5-yl]methyl}-4-methyl-1,3-oxazolidine-2-one

A) Methyl 2-(4-Chloro-2-fluorophenoxy)pyrimidine-5-carboxylate

A mixture of methyl 2-chloropyrimidine-5-carboxylate (5.00 g), 4-chloro-2-fluorophenol (3.08 mL), potassium carbonate (6.01 g), and MeCN (60 mL) was stirred for 16 hours in a nitrogen atmosphere at room temperature. The mixture was diluted using ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using water and a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure. The residue was crystallized using hexane, whereupon the compound of the heading (7.39 g) was obtained.

MS: [M+H]⁺283.0.

[0223]

B) 2-(4-Chloro-2-fluorophenoxy)pyrimidine-5-carboxylic acid

A 2 M sodium hydroxide aqueous solution (14.4 mL) was added to a mixture of methyl 2-(4-chloro-2-fluorophenoxy)pyrimidine-5-carboxylate (7.39 g) and THF (50 mL) at room temperature, and the mixture was stirred for 16 hours. After concentrating the reaction mixture under reduced pressure, this was diluted using water (30 mL) and neutralized using 1 M hydrochloric acid (29 mL). The obtained precipitate was filtered out and washed using water, whereupon the compound of the heading (6.35 g) was obtained.

MS: [M-H]⁺266.8.

[0224]

C) (2-(4-Chloro-2-fluorophenoxy)pyrimidine-5-yl)methanol

Isobutyl chloroformate (3.67 mL) and 4-methylmorpholine (3.89 mL) were added to a mixture of 2-(4-chloro-2-fluorophenoxy)pyrimidine-5-carboxylic acid (6.33 g) and THF (100 mL) at 0°C,

and the mixture was stirred for 1 hour at the same temperature. Sodium borohydride (2.23 g) and water (25 mL) were dripped therein at 0°C, and the mixture was stirred for an additional 16 hours at room temperature. The mixture was diluted using ethyl acetate and water and extracted using ethyl acetate. The organic layer was washed using water and a saturated saline solution, dried using sodium sulfate, passed through an NH silica gel pad, and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane) and crystallized using IPE, whereupon the compound of the heading (2.80 g) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 4.50 (2H, d, J = 5.3 Hz), 5.39 (1H, t, J = 5.7 Hz), 7.33-7.40 (1H, m), 7.42-7.51 (1H, m), 7.65 (1H, dd, J = 10.5, 2.3 Hz), 8.59 (2H, s).

[0225]

D) 5-(Bromomethyl)-2-(4-chloro-2-fluorophenoxy)pyrimidine

Phosphorous tribromide (1.15 mL) was added to a mixture of (2-(4-chloro-2-fluorophenoxy)pyrimidine-5-yl)methanol (2.80 g) and THF (25 mL) at 0°C, and this was stirred for 16 hours at room temperature. The mixture was diluted using ethyl acetate, and this solution was washed using a sodium hydrogen carbonate aqueous solution and a saturated saline solution and dried using sodium sulfate. The residue was purified using silica-gel column chromatography (ethyl acetate / hexane) and crystallized using hexane, whereupon the compound of the heading (2.22 g) was obtained.

MS: [M+H]⁺316.9.

[0226]

E) (4S)-3-{[2-(4-Chloro-2-fluorophenoxy)pyrimidine-5-yl]methyl}-4-methyl-1,3-oxazolidine-2-one

A 1.6 M butyllithium hexane solution (0.637 mL) was added to a mixture of (S)-4-methyloxazolidine-2-one (0.103 g) and THF (8 mL) at -78°C, and this was stirred for 30 minutes at 0°C. 5-(Bromomethyl)-2-(4-chloro-2-fluorophenoxy)pyrimidine (0.323 g) was added to the mixture, and this was stirred for 60 hours at room temperature. The mixture was diluted using ethyl acetate and water and afterward extracted using ethyl acetate. The organic layer was washed using a saturated saline solution. Afterward, this was dried using sodium sulfate and concentrated under reduced pressure. The residue was purified using silica-gel column chromatography (NH, ethyl acetate / hexane) and recrystallized using ethyl acetate / heptane, whereupon the compound of the heading (0.233 g) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.18 (3H, d, J = 6.0 Hz), 3.77-3.87 (2H, m), 4.27 (1H, d, J = 15.0 Hz), 4.35-4.50 (2H, m), 7.34-7.41 (1H, m), 7.43-7.51 (1H, m), 7.66 (1H, dd, J = 10.4, 2.4 Hz), 8.63 (2H, s).

[0227]

The example compounds are given in the following tables. In the tables, MS indicates a measured value. The compounds of examples 1 to 12, 14 to 16, 18 to 36, 39 to 44, 46 to 48, and 50 were produced according to the methods given in the above examples or methods equivalent thereto.

5 [0228] [Table 1-1]

Example no.	IUPAC name	Structural formula	Salt	MS
1	5-Methyl-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one			296.3
2	5-Methyl-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one (optical isomer)			296.2
3	5-Methyl-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one (optical isomer)			296.2
4	5-Methyl-1-{{5-(4-methylphenoxy)pyrazine-2-yl}methyl}pyrrolidine-2-one			298.2
5	5-Methyl-1-{{2-(4-methylphenoxy)pyrimidine-5-yl}methyl}pyrrolidine-2-one			298.2
6	(4S,5S)-4-Hydroxy-5-methyl-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one			312.2
7	(4S,5S)-5-Ethyl-4-hydroxy-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one			326.2
8	5-Methyl-1-{{5-(4-methylphenoxy)pyrimidine-2-yl}methyl}pyrrolidine-2-one			298.1
9	(4S,5S)-1-{{4-(4-Fluorophenoxy)phenyl}methyl}-4-hydroxy-5-methylpyrrolidine-2-one			316.1
10	(4R,5S)-4-Hydroxy-5-methyl-1-{{4-(4-methylphenoxy)phenyl}methyl}pyrrolidine-2-one			312.2

Example no.	IUPAC name	Structural formula	Salt	MS
11	(4S,5R)-4-Hydroxy-5-methyl-1-{[4-(4-methylphenoxy)phenyl]methyl}pyrrolidine-2-one			312.2
12	(4R,5R)-4-Hydroxy-5-methyl-1-{[4-(4-methylphenoxy)phenyl]methyl}pyrrolidine-2-one			312.2
13	(4S,5S)-4-Hydroxy-5-methyl-1-{[6-(4-methylphenoxy)pyridine-3-yl]methyl}pyrrolidine-2-one			313.2
14	(4S,5S)-4-Hydroxy-5-methyl-1-{[6-(4-methylphenoxy)pyridine-3-yl]methyl}pyrrolidine-2-one		HCl	313.2
15	(4S,5S)-4-Hydroxy-5-methyl-1-{[2-(4-methylphenoxy)pyrimidine-5-yl]methyl}pyrrolidine-2-one			314.2
16	(4S,5S)-4-Hydroxy-5-methyl-1-{[5-(4-methylphenoxy)pyridine-2-yl]methyl}pyrrolidine-2-one			313.2
18	(4S)-4-Methyl-3-{[4-(4-methylphenoxy)phenyl]methyl}-1,3-oxazolidine-2-one			298.2
19	(4S,5S)-4-Hydroxy-5-methyl-1-{[5-(4-methylphenoxy)pyrazine-2-yl]methyl}pyrrolidine-2-one			314.2
20	(4S)-4-Methyl-3-{[6-(4-methylphenoxy)pyridine-3-yl]methyl}-1,3-oxazolidine-2-one			299.2

[Table 1-3]

Example no.	IUPAC name	Structural formula	Salt	MS
21	(5S)-5-Methyl-1-{{6-(4-methylphenoxy)pyridine-3-yl}methyl}pyrrolidine-2-one			297.2
22	(5S)-5-Methyl-1-{{2-(4-methylphenoxy)pyrimidine-5-yl}methyl}pyrrolidine-2-one			298.2
23	(4S)-3-{{2-(2-Fluoro-4-methylphenoxy)pyrimidine-5-yl}methyl}-4-methyl-1,3-oxazolidine-2-one			318.2
24	(4S)-4-Methyl-3-{{2-(2,4,6-trifluorophenoxy)pyrimidine-5-yl}methyl}-1,3-oxazolidine-2-one			340.1
25	(4S)-3-{{6-(2-Fluoro-4-methylphenoxy)pyridine-3-yl}methyl}-4-methyl-1,3-oxazolidine-2-one			317.2
26	(4S,5S)-1-{{6-(2-Fluoro-4-methylphenoxy)pyridine-3-yl}methyl}-4-hydroxy-5-methylpyrrolidine-2-one			331.2
27	(4S,5S)-4-Hydroxy-5-methyl-1-{{6-(2,4,6-trifluorophenoxy)pyridine-3-yl}methyl}pyrrolidine-2-one			353.1
28	(4S)-4-Methyl-3-{{6-(2,4,6-trifluorophenoxy)pyridine-3-yl}methyl}-1,3-oxazolidine-2-one			339.2
29	1-{{6-(4-Methylphenoxy)pyridine-3-yl}methyl}-5-(trifluoromethyl)pyrrolidine-2-one			351.2
30	(4S)-4-Methyl-3-{{2-(4-methylphenoxy)pyrimidine-5-yl}methyl}-1,3-oxazolidine-2-one			300.2

Example no.	IUPAC name	Structural formula	Salt	MS
31	(4S,5S)-1-{{6-(2,6-Difluoro-4-methylphenoxy)pyridine-3-yl}methyl}-4-hydroxy-5-methylpyrrolidine-2-one			349.2
32	(4S)-3-{{2-(2,6-Difluoro-4-methylphenoxy)pyrimidine-5-yl}methyl}-4-methyl-1,3-oxazolidine-2-one			336.2
33	(5S)-5-Methyl-1-{{6-(2,4,6-trifluorophenoxy)pyridine-3-yl}methyl}imidazolidine-2-one			338.1
34	(4R,5S)-3,3-Difluoro-4-hydroxy-5-methyl-1-{{6-(2,4,6-trifluorophenoxy)pyridine-3-yl}methyl}pyrrolidine-2-one			389.1
35	(5S)-1-{{6-(2,4-Difluorophenoxy)pyridine-3-yl}methyl}-5-methylimidazolidine-2-one			320.2
36	(4R,5S)-1-{{6-(2,4-Difluorophenoxy)pyridine-3-yl}methyl}-3,3-difluoro-4-hydroxy-5-methylpyrrolidine-2-one			371.1
37	(4S,5S)-1-{{6-(2,4-Difluorophenoxy)pyridine-3-yl}methyl}-4-hydroxy-5-methylpyrrolidine-2-one			335.2
38	(4S,5S)-1-({6-[4-(Difluoromethyl)-2-fluorophenoxy]pyridine-3-yl}methyl)-4-hydroxy-5-methylpyrrolidine-2-one			367.1
39	4-(Fluoromethyl)-3-{{6-(2-fluoro-4-methylphenoxy)pyridine-3-yl}methyl}-1,3-oxazolidine-2-one			335.1
40	4-(Difluoromethyl)-3-{{6-(2-fluoro-4-methylphenoxy)pyridine-3-yl}methyl}-1,3-oxazolidine-2-one			353.1

Example no.	IUPAC name	Structural formula	Salt	MS
41	(4S,5S)-1-({6-[2-Fluoro-4-(trifluoromethyl)phenoxy]pyridine-3-yl}methyl)-4-hydroxy-5-methylpyrrolidine-2-one			385.1
42	(5S)-1-({2-[4-(Difluoromethyl)-2-fluorophenoxy]pyrimidine-5-yl}methyl)-5-methylpyrrolidine-2-one			352.2
43	(4S,5S)-1-{{6-[4-(4-Chloro-2-fluorophenoxy)pyridine-3-yl]methyl}-4-hydroxy-5-methylpyrrolidine-2-one			351.1
44	(5S)-1-{{2-[2-(2-Fluoro-4-methylphenoxy)pyrimidine-5-yl]methyl}-5-methylpyrrolidine-2-one			316.1
45	(5S)-1-{{2-[2,4-Difluorophenoxy]pyrimidine-5-yl]methyl}-5-methylpyrrolidine-2-one			320.1
46	(5S)-1-{{2-[4-(4-Chloro-2-fluorophenoxy)pyrimidine-5-yl]methyl}-5-methylpyrrolidine-2-one			336.1
47	(5S)-1-({6-[4-(Difluoromethyl)-2-fluorophenoxy]pyridine-3-yl}methyl)-5-methylpyrrolidine-2-one			351.1
48	(5S)-1-{{6-[2,4-Difluorophenoxy]pyridine-3-yl]methyl}-5-methylpyrrolidine-2-one			319.1
49	(4S)-3-{{2-[4-(4-Chloro-2-fluorophenoxy)pyrimidine-5-yl]methyl}-4-methyl-1,3-oxazolidine-2-one			338.1
50	(4S)-3-({6-[4-(Difluoromethyl)-2-fluorophenoxy]pyridine-3-yl}methyl)-4-methyl-1,3-oxazolidine-2-one			353.1

[0233]

Test example: NR2B Ca^{2+} influx assay

To confirm the “antagonistic action against an NMDA receptor that includes the NR2B subunit” had by the compound of the present invention, human embryonic kidney cells that express an “NMDA receptor constituted by four subunits made of two sets of heterodimers of NR1 and NR2B”—specifically, HEK 293 cells that express human glutamate ionotropic receptor NMDA type subunit 1 (GRIN1) and human glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B)—were used to measure an activation suppression effect of this receptor.

The HEK 293 cells that express GRIN1 and GRIN2B were purchased from ChanTest (human NMDA (NR1/NR2B) receptor-expressing, stable replicating cell line (HEK 293) catalog no. CT6121).

Note that intracellular calcium-ion (Ca^{2+}) influx caused by glycine and glutamic acid respectively binding to NR1 and NR2B was used as an indicator of NMDA receptor activation.

The HEK 293 cells that express GRIN1 and GRIN2B were cultured in a cell culture flask by an incubator (37°C, in 5% CO_2) using a DMEM/F-12 (Cosmo Bio, 10-092-CM) medium into which were added 10% FBS (fetal bovine serum, Ausgene), 100 units/mL penicillin, 100 $\mu\text{g/mL}$ streptomycin, 500 $\mu\text{g/mL}$ neomycin, 100 $\mu\text{g/mL}$ Zeocin (registered trademark of Invitrogen), and 5 $\mu\text{g/mL}$ blasticidin.

On the day before the assay, the cells were peeled from the flask using trypsin, suspended in a seeding medium (DMEM (Invitrogen, 31053) into which were added 10% FBS, 100 units/mL penicillin, and 100 $\mu\text{g/mL}$ streptomycin) so as to be 8×10^5 cells/mL, seeded at 25 μL per well in a 384-well plate (Falcon, 356663) so as to be 20,000 cells/well, and cultured overnight using the incubator. On the day of the assay, tetracycline (Wako Pure Chemical, 209-16561) was diluted so as to be 2 $\mu\text{g/mL}$ in the seeding medium. This was added at 25 $\mu\text{L/well}$ to the plate into which the cells were seeded, and this was cultured for 2 hours using the incubator. Afterward, the medium was removed and washed using an assay buffer (137 mM NaCl, 4 mM KCl, 1.8 mM CaCl_2 , 10 mM HEPES (pH 7.2), 10 mM glucose, 0.1% BSA) at 50 $\mu\text{L/well}$. Next, a loading buffer (buffer wherein 2.5 μM Fluo-4 AM, 2 mM amaranth, and 1 mM tartrazine are added to the assay buffer) was added at 25 $\mu\text{L/well}$, and this was incubated using the incubator for 30 minutes and for 15 minutes at room temperature. Solutions wherein the example compounds were diluted using the above assay buffer so as to be 30 μM (final concentration 10 μM) were added at 25 $\mu\text{L/well}$, and these were left standing for 15 minutes at room temperature. Using FDSS7000EX/ μCELL (Hamamatsu Photonics), an assay buffer including 30 μM glutamic acid and 30 μM glycine was added at 25 $\mu\text{L/well}$, and a fluorescence signal of an excitation wavelength of 480 nm and an emission wavelength of 540 nm was measured every 3 seconds for 5 minutes. Inhibited activity

was calculated as a relative activity value (inhibition rate) wherein relative to an integrated value of fluorescence values of each well, an integrated value of fluorescence values of a well into which an assay buffer including no glutamic acid and glycine was added was defined as 100% inhibition. The results are given in table 2.

5 [0234] [Table 2]

Example	% inhibited (10 μ M)	Example	% inhibited (10 μ M)
1	99	26	97
2	98	27	97
3	99	28	96
4	93	29	93
5	91	30	90
6	97	31	97
7	98	32	92
8	53	33	97
9	96	34	97
10	94	35	96
11	91	36	97
12	93	37	97
13	97	38	95
14	96	39	92
15	90	40	95
16	95	41	95
18	98	42	97
19	82	43	98
20	97	44	97
21	98	45	96
22	95	46	97
23	94	47	99
24	93	48	98
25	96	49	97
		50	98

[0235]

As indicated in table 2 above, the compound of the present invention suppressed intracellular calcium-ion (Ca^{2+}) influx in an NMDA receptor that includes the NR2B subunit. That is, it was confirmed that the compound of the present invention has an antagonistic action against an NMDA receptor that includes the NR2B subunit.

[0236]

Preparation example 1 (production of capsule)

- 1) Compound of example 1 30 mg
- 15 2) Fine cellulose powder 10 mg
- 3) Lactose 19 mg

4) Magnesium stearate	1 mg
Total	60 mg

1), 2), 3), and 4) are mixed and filled in a gelatin capsule.

[0237]

5 Preparation example 2 (production of tablet)

1) Compound of example 1	30 g
2) Lactose	50 g
3) Corn starch	15 g
4) Carboxymethyl cellulose calcium	44 g

10	5) Magnesium stearate	1 g
	1,000 tablets	Total 140 g

The entirety of 1), 2), and 3) and 30 g of 4) are kneaded using water, vacuum-dried, and graded. 14 g of 4) and 1 g of 5) are mixed into this graded powder, and this is made into tablets using a tableting machine. In this manner, 1,000 tablets containing 30 mg of the compound of example 1 per tablet are obtained.

[Industrial Applicability]

[0238]

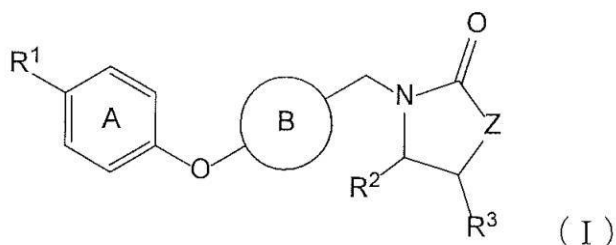
The compound of the present invention can have an antagonistic action against an NMDA receptor that includes the NR2B subunit and is anticipated to be useful as a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, a symptom peripheral to dementia, or the like.

Scope of Patent Claims

[Claim 1]

A compound represented by formula (I):

[Chem. 1]



[in the formula,

R¹ indicates a C₁₋₃ alkyl group that may be substituted by a fluorine atom or indicates a halogen atom;

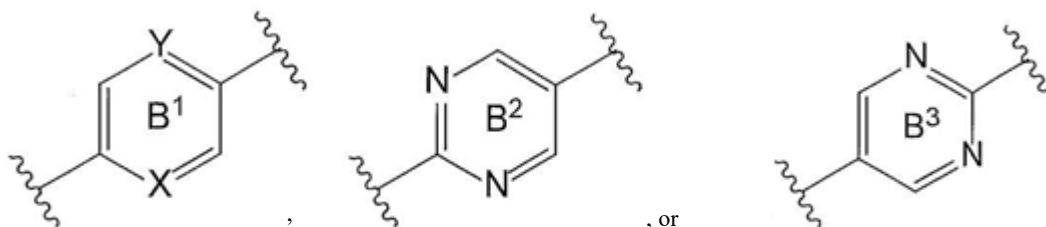
10 R² indicates a C₁₋₃ alkyl group that may be substituted by a fluorine atom;

R³ indicates a hydrogen atom or a hydroxy group;

ring A indicates a benzene ring that may be further substituted;

ring B

indicates



[Chem. 2]

(in the formula,

X and Y each independently indicate a carbon atom or a nitrogen atom;

20 ring B¹ indicates a benzene ring, a pyridine ring, or a pyrazine ring that may each be further substituted; and

ring B² and ring B³ each indicate a pyrimidine ring that may be further substituted); and

Z indicates CH₂, CF₂, O, or NH]

or a salt thereof.

25 [Claim 2]

A pharmaceutical, comprising the compound according to claim 1 or a salt thereof.

[Claim 3]

The pharmaceutical according to claim 2, wherein the pharmaceutical is an antagonist against an NMDA receptor that includes the NR2B subunit.

[Claim 4]

5 The pharmaceutical according to claim 2, wherein the pharmaceutical is a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, or a symptom peripheral to dementia.

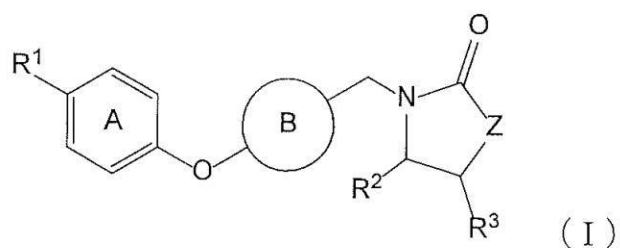
Abstract

[Abstract]

[Problem] To provide a heterocyclic compound that can have an antagonistic action against an NMDA receptor that includes the NR2B subunit and is anticipated to be useful as a preventive or therapeutic agent for depression, bipolar disorder, migraine, pain, a symptom peripheral to

5 dementia, or the like.

[Resolution Means] A compound represented by formula (I):



10 [in the formula, the symbols are as described in the specification]
or a salt thereof.

[Selected FIG.] None

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 15496-19-304	FOR FURTHER ACTION		See item 4 below
International application No. PCT/IB2020/000962	International filing date (<i>day/month/year</i>) 12 November 2020 (12.11.2020)	Priority date (<i>day/month/year</i>) 14 November 2019 (14.11.2019)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant TAKEDA PHARMACEUTICAL COMPANY LIMITED			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a). 2. This REPORT consists of a total of 7 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																										
3. This report contains indications relating to the following items: <table border="0"> <tr> <td>☒</td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td>☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td>☐</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td>☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td>☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td>☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td>☒</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td>☒</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> 4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).			☒	Box No. I	Basis of the report	☐	Box No. II	Priority	☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	☐	Box No. IV	Lack of unity of invention	☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	☐	Box No. VI	Certain documents cited	☒	Box No. VII	Certain defects in the international application	☒	Box No. VIII	Certain observations on the international application
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☒	Box No. VII	Certain defects in the international application																								
☒	Box No. VIII	Certain observations on the international application																								

	Date of issuance of this report 17 May 2022 (17.05.2022)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Cécile Chatel e-mail ro.ib@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2020/000962

International filing date (day/month/year)
12.11.2020

Priority date (day/month/year)
14.11.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D207/263 C07D401/06 C07D403/06 C07D413/06 A61P25/28 A61P25/06 A61K31/4015

Applicant
TAKEDA PHARMACEUTICAL COMPANY LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Kleidermigg, Oliver

Telephone No. +49 89 2399-0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>5-7</u>
	No: Claims	<u>1-4, 8-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

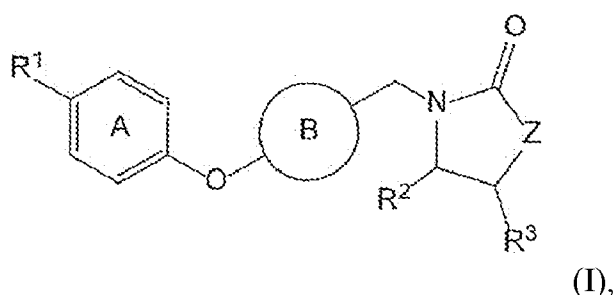
see separate sheet

ad Item V

Reference is made to the following documents:

- D1 WO 01/30330 A2 (MERCK SHARP & DOHME [GB]; KULAGOWSKI JANUSZ JOZEF [GB]) 3 May 2001 (2001-05-03)
- D2 WO 2009/004430 A1 (PFIZER [US]; DUPLANTIER ALLEN JACOB [US] ET AL.) 8 January 2009 (2009-01-08)
- D3 US 6 420 415 B1 (YAMASHITA TOSHIRO [JP] ET AL) 16 July 2002 (2002-07-16)
- D4 EP 1 500 658 A1 (TAKEDA PHARMACEUTICAL [JP]) 26 January 2005 (2005-01-26)

The present application is directed to compound of formula (I):



or a salt thereof as well as pharmaceutical compositions containing it and its medical use.

Novelty

None of the cited documents D1-D4 discloses compounds showing the structural features of the compounds of claim 1. The same applies to claim 5-7.

Consequently, the subject matter of claim 1 is novel. Since claims 2-4, 8-14 directly or indirectly refer to the compounds of claim 1, those claims are novel by analogy.

Inventive step

D1 represents the closest prior art.

D1 differs from the subject matter of claim 1 insofar that it discloses NMDA antagonists of formula



In view of the distinguishing features with respect to the closest prior art of D1 the objective technical problem may be considered as the provision of alternative NMDA antagonists.

The solution is given in the independent claims and concerns the compounds of formula (I).

However, on the basis of the very limited biological results and the extremely minor variations in the structure of the tested examples, compared to all possible variations claimed, the applicant did not unambiguously show that all claimed compounds have the same effect (Article 33(3) PCT) and that the technical problem has been solved over the full scope of claim 1. Consequently, the subject matter of claim 1 is not considered to be inventive. Claims 2-5, 8-14 are presently not considered to add any features which may establish inventive activity.

Consequently, the claims should be limited to the tested examples like claims 5-7.

Medical use

Claims 12, 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 12, 13 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

ad Item VII

The phrase "incorporated by reference herein in its entirety" e.g. on page 1 violates Rule 9.1 iv) PCT.

ad Item VIII

Although claims 1, 5, 6, 7 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.



**Superintendencia de
Industria y Comercio**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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CAROLINA MERCEDES DAZA MONTALVO

CC: 66.783.790

Pago PSE No: 1196019

CUS: 1979282824

Patente PCT

ANTAGONISTAS HETEROCÍCLICOS DE NMDA

Detalle del pago

Id.	Rentístico	Concepto y Servicio	Cant.	Val. Unit.	Subtotal
1	50005-01-03	Modificaciones / Correcciones al registro Patente PCT (DESCUENTO INTERNET)	1	\$ 225,000	\$ 225,000
2	50005-01-02	REIVINDICACION MODELO DE UTILIDAD (A PARTIR DE LA UNDECIMA REIVINDICACION DCT. LINEA)	32	\$ 56,500	\$ 1,808,000
3	50005-01-01	Solicitud examen de patentabilidad Patente PCT (DESCUENTO INTERNET)	1	\$ 1,522,000	\$ 1,522,000
TOTAL					\$ 3,555,000