

Señora

Directora de la Dirección de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Industria y Turismo

E. S. D.

Re.: Expediente No. **NC2019/0013706**

Solicitud de registro Patente PCT entrada en Fase Nacional, para:

**“COMPUESTOS Y COMPOSICIONES PARA INDUCIR LA
CONDROGÉNESIS”.**

Solicitante: **NOVARTIS AG**

RESPUESTA OFICIO DE FORMA

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante del asunto citado en la referencia, en atención a su oficio **No. 14171** notificado el 24 de diciembre de 2019, me permito dar respuesta al mismo de la siguiente manera:

1. Capítulo I o II

Se adjunta al presente memorial el IPEA (International Preliminary Report on Patentability), correspondiente a la solicitud estudiada, con su respectiva traducción al castellano.

2. Conclusión

Teniendo en cuenta lo anterior, es posible establecer que se cumplen los requisitos formales dispuestos en el artículo 39 de la Decisión 486.

3. Anexos

- IPEA junto con su traducción al español

Señora Directora,



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 57749-WO-PCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/IB2018/054123	International filing date (day/month/year) 07.06.2018	Priority date (day/month/year) 09.06.2017	
International Patent Classification (IPC) or national classification and IPC INV. C07D493/08			
Applicant Novartis AG			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>28</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ 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			
Date of submission of the demand 09.04.2019		Date of completion of this report 18.09.2019	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Kirsch, Cécile Telephone No. +49 89 2399-2191	



Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-121 as originally filed

122-146 filed in electronic form on

11-07-2019

Claims, Numbers

1-23 as originally filed

☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☒ the description, pages 122
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2018/054123

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 01.08.2019 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-23</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>7</u>
	No: Claims	<u>1-6, 8-23</u>
Industrial applicability (IA)	Yes: Claims	<u>1-23</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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

Reference is made to the following document:

D1: WO 2015/175487 cited in the application

The present application deals with N-cyclyl-3-heteroaryl-7-oxabicyclo[2.2.1]heptane-2-carboxamide and N-cyclyl-7-heteroaryl-8-oxatricyclo[3.2.1.0^{2,4}]octane-6-carboxamide derivatives for treating or preventing arthritis and joint injury and for inducing chondrogenesis. It also relates to intermediate compounds useful in the preparation of the active compounds.

Re Item I

Basis of the report

The applicant has provided amendments in the description only.

The amendments filed introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

In Table 1, original compounds 2-30 have been renumbered as compounds 3-31 respectively.

On the basis of examples 3-31 and the nomenclature disclosed therein, the renumbering in Table 1 is seen as the correction of an obvious error because the nomenclature in Table 1 was not consistent with the nomenclature in the corresponding examples.

In Table 1, original compound 31 has been renumbered as compound 31A. Since the nomenclature in Table 1 did not correspond to example 31, the renumbering is allowable because it is not associated with any new teaching.

However, the new entry for compound 2 in Table 1 is not allowable. There is no support for the biological data associated with this compound. In this respect, the applicant refers to the priority document as support for the modification. However, it is not permissible to add to an international application matter present only in the priority document for that application (GL/PCT-EPO H-II, 2.2.4).

For these reasons, the proposed modification for example 2 in Table 1 contravenes the requirements of Article 34(2)(b) PCT and is not allowable.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claims 19-23 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 19-23 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compounds.

1. Novelty, Article 33(2) PCT

Document D1 discloses 7-oxabicyclo[2.2.1]heptane-2-carboxamide derivatives and their use for the treatment of arthritis or joint injury. The subject-matter of D1 has been excluded by means of two disclaimers (R6 and R7 of D1 are H or alkyl). The active compounds, the pharmaceutical compositions and the medical uses are also novel. Since the disclaimers also apply to the intermediate compounds, these intermediates are also novel with regard to D1.

Novelty is acknowledged vis-à-vis D1.

2. Inventive step, Article 33(3) PCT

2.1. Document D1 represents the closest prior art. The compounds of D1 differ from the claimed subject-matter due to the combination of substituents at positions 5 and 6.

2.2. The effect associated with this difference is the conservation of the biological properties.

The problem to be solved by the present application is seen in the provision of further 7-oxabicyclo[2.2.1]heptane-2-carboxamide derivatives for use for the treatment of arthritis and joint injury.

According to table 3, not all compounds are active (% Efficacy is 0 or close to 0 for a number of compounds). It is therefore apparent that the claimed subject-matter has not been solved on the whole claimed scope.

2.3. It is apparent from D1 that the disclaimed compounds of formula I exhibit the claimed activity. It is established case law that if a disclaimer can be used to make an inventive teaching novel, it cannot make an obvious teaching inventive.

In the present case, the claimed compounds are structurally closely related to the compounds of D1. In the pharmaceutical field, the motivation to make new compounds derives from the expectation that structurally similar compounds would possess similar activity. One skilled in the art would thus be motivated to prepare products related the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating arthritis and joint injury.

Therefore, the claimed compounds are merely obvious alternatives of the active compounds disclosed in document D1. The claimed subject-matter thus lacks an inventive step.

2.4. The chirality of claims 2 and 3 is already disclosed in claim 10 of D1. According to claims 4 to 6, preferred embodiments at positions 4 and 6 have hydrogen atoms at these positions which comes very close to the compounds of D1. The embodiments of claims 8 to 9 are preferred according to claims 4-5 and 11-13 of D1. The embodiments of claims 10 and 11 correspond to the teaching of claims 6-7 and 14-15 of D1. The specific compounds of claim 12 are also closely related to the exemplified compounds of D1. Hydrates, as in claim 13, are already taught by D1, see page 40 last paragraph to page 41, first paragraph. The intermediate compound according to claims are likewise used in D1, see e.g. Formula 2a and synthetic examples. Pharmaceutical compositions and medical uses are disclosed in claims 17, 20 and 23-25 and lack also an inventive step. Combinations are disclosed on page 59, one but last paragraph of D1.

2.5. The subject-matter of claims 7 wherein the carbon atoms at positions 5 and 6 are linked to form a cyclopropyl is not rendered obvious by the teaching of D1 and is considered inventive for those compounds which credibly solve the problem posed.

Re Item VII

Certain defects in the international application

The expression "herein incorporated by reference" as well as similar expressions should be deleted from the description.

Re Item VIII

Certain observations on the international application

1. Claim 12 contains references to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
2. The subject-matter described on page 17, embodiment 29, 5th and 11th compounds (unsaturation in the ring) does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.
3. The vague and imprecise statement in the description on page 146, last paragraph, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
4. A compound "for cartilage repair" (see second part of claim 17) is construed as referring to a compound suitable for said use and is not limiting on the compound. Such wording would therefore seem redundant vis-à-vis claim 1.
5. Compounds 3 and 31A are the same (same chemical name). However, the biological data differ in Table 1. It follows a lack of clarity.

In re application of: Novartis AG Application No.: PCT/IB2018/054123 International Filing date: 7 June 2018 For: COMPOUNDS AND COMPOSITIONS FOR INDUCING CHONDROGENESIS	<u>REPLY TO WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY</u>
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European Patent Office
 D-80298 Munich

Attn: Cécile Kirsch

Dear Madam:

Applicant submits this reply to the Written Opinion of the International Preliminary Examining Authority (IPEA) dated 17 May 2019. The IPEA indicated that “[o]n the basis of examples 4-30 and the nomenclature disclosed therein, the renumbering in Table 1 is seen as the correction of an obvious error.” The IPEA also indicated that the “renumbering of 31 to 2 and 2 and 3 to 3 and 4 respectively does not obviously derives [sic] from the application as filed.”

New Example No. 2 and the associated activity data are supported by Example No. 2 in Table 3 of U.S. provisional application serial no. 62/517,394 filed 9 June 2017. The nomenclature in new Example No. 2 is also in accordance with the nomenclature in corresponding Example 2 of the priority document. Furthermore, renumbered Ex No. 3 and 4 (formerly Ex No. 2 and 3) are supported by corresponding Examples 3 and 4 and the nomenclature disclosed therein.

For clarity and to correct obvious numbering errors, Example Nos. 4-30 as originally filed were renumbered to Ex Nos. 5-31, respectively. The amendment is supported by the nomenclature in corresponding Examples 5-31. Example No. 31 as originally filed has been renumbered to new Ex No. 31A, to avoid duplicate numbering.

Based on the above, Applicant respectfully requests that the IPEA amend the application by replacing pages 122-146 of the description with the replacement sheets in Appendix A. The replacement sheets correct obvious typographical errors and do not contain new matter:

- New Ex No. 2 has been added, in accordance with Example No. 2 in Table 3 of the priority document;
- Ex No. 2 and 3 as originally filed have been renumbered to Ex Nos. 3 and 4, respectively, in accordance with corresponding Examples 3 and 4;

- Ex Nos. 4-30 as originally filed have been renumbered to Ex Nos. 5-31, respectively, in accordance with corresponding Examples 5-31;
- Ex No. 31 as originally filed has been renumbered to Ex No. 31A, to distinguish between renumbered Ex No. 31 (originally Ex. No. 30);
- “rac-“ was added before the compounds names in Ex Nos. 2, 11, 12, 24, 43, 47, 49, 52, 53, 54, 77, 90, 121, 122, 126, 139 and 142, in accordance with the corresponding examples

Respectfully submitted,

/Emily T. Wu/

Emily T. Wu
Reg. No. 46,473

Date: July 11, 2019

Customer No. 29490
The Genomics Institute of the
Novartis Research Foundation (GNF)
Office: (858) 812-1539

APPENDIX A

Replacement Sheets 122-146

Alkaline Phosphatase Staining and Quantitation in C3H10T1/2

To initiate differentiation in C3H10T1/2, Clone 8 (ATCC cat# CCL-226), 4,000 cells were plated / well in 384 Perkin Elmer CellCarrier Ultra plate in DMEM/High glucose (HyClone cat# SH30022.01) containing 10% FBS and 1x Antibiotic/Antimycotic (HyClone cat# SV30079.01).
 5 After 24 hours the the test compound was then added to each well at the indicated dose. The cultures were grown at 37°C for 6 days.

To detect the presence of hypertrophic cells, C3H10T1/2 were fixed with 4% paraformaldehyde and Hoeschst dye for 20 minutes, rinsed in PBS, then stained with Fast Blue RR Salt with Naphthol AS-MX Phosphate Alkaline Solution. Once cells were observed to turn
 10 blue, after approximately 3 hours at 37°C, they were washed with PBS six times.

The ALP staining was imaged by fluorescecent microscopy, using the 561 wavelength, and / or quantified by high content imaging with the ImageXpress Micro Confocal (Molecular Devices, Sunnyvale, CA). Data analyses were performed with the customized multiwavelength cell-scoring application looking at the number of ALP positive cells per well.

15 Calcium Flux assay and Quantitation

NHACs were plated in 1536 Greiner plate at 2000 cells/well in 4ul volume. 24 hours later, 4ul of Calcium 5 dye solution (Hank's Balanced Salt/HEPES buffer containing 5mM of Probenecid) was then added and incubated for 1 hour at room temperature. Fluorescence readings at excitation wavelength of 470-495nm and emission wavelength of 515-575nm were done using
 20 FLIPR high-throughput screening system (Molecular Devices, Sunnyvale, CA). The test compound was then added to each well at the indicated dose. Signal was measured prior compound dispense and after using a first interval of 1 second for 60 reads and second interval of 3 second for 20 reads. Data was analyzed using Molecular Devices ScreenWorks® Software.

The activity of the compounds of the present invention in the following assays are
 25 summarized in Table 3. Legend: (A) calcium flux assay; (B) collagen Type II assay; (C) alkaline phosphatase assay in NHAC; and (D) alkaline phosphatase assay in C3H10T1/2.

Table 3

Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
1	(1S,2S,4R,5R,6S,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2-methoxypyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	3.4 (164)			
2	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(6-methoxypyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
3	(1S,2S,4R,5R,6S,7S)-N-(6-methoxypyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	0.30 (45)			
4	(1R,2R,4S,5S,6R,7R)-N-(6-methoxypyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
5	(1R,2S,3S,4R,5S)-N-(4,5-dichloropyridin-2-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (28)			
6	(1R,2S,3S,4R,5S)-N-(5-chloro-6-methylpyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (18)			
7	(1R,2S,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (17)			
8	(1S,2R,3R,4S,5R)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
9	(1R,2S,3S,4R,5S)-5-hydroxy-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (50)		>31 (62)	>20 (16)
10	(1S,2S,3S,4S,6R)-6-hydroxy-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
11	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
11a	(1R,2S,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (55)			
12	<i>rac</i> -(1R,2S,3S,4R,5S)-5-hydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (27)			
12a	(1R,2S,3S,4R,5S)-5-hydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	0.27 (98)	2.9 (91)	48 (65)	>20 (6)
13	(1S,2S,3S,4S,6R)-6-hydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (22)			
14	(1R,2S,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	4.5 (68)			
15	(1R,2S,3S,4R,5R)-5-fluoro-N-(6-methoxypyridin-3-yl)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	8.3 (115)			
16	(1R,2S,3S,4R,5R)-5-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
17	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	21 (105)			
18	(1R,2S,3S,4R,5S)-5-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
19	(1R,2S,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
20	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	25 (258)			
21	(1R,2S,3S,4R,5S)-3-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-5-fluoro-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (5)			
22	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	27 (159)			
23	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-fluoropyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	4.2 (128)			
24	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (54)			
24a	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	6.1 (99)	0.78 (29)	30 (100)	>20 (28)
24b	(1R,2R,4S,5S,6R,7R)-N-(3,4-dichlorophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
25	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-methoxypyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	11 (71)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
26	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-fluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	17 (52)			
27	(1S,2S,4R,5R,6S,7S)-7-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	23 (54)			
28	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	13 (120)		34 (71)	>20 (48)
29	(1R,2R,4S,5S,6R,7R)-N-(3,4-dichlorophenyl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	23 (167)			
30	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (6)			
31	(1R,2R,4S,5S,6R,7R)-N-(3,4-dichlorophenyl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	10 (133)			
31A	(1S,2S,4R,5R,6S,7S)-N-(6-methoxypyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
32	(1S,2S,4R,5R,6S,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	13 (143)			
33	(1S,2S,4R,5R,6S,7S)-N-(6-methoxypyridin-3-yl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	4.6 (49)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
34	(1S,2S,4R,5R,6S,7S)-7-(2,3-difluoropyridin-4-yl)-N-(6-methoxypyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (3)			
35	(1S,2S,4R,5R,6S,7S)-N-(6-methoxypyridin-3-yl)-7-[6-(trifluoromethyl)pyridin-2-yl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
36	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-fluoropyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	8.6 (124)			
37	(1S,2S,4R,5R,6S,7S)-7-(pyrimidin-5-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (26)			
38	(1S,2S,4R,5R,6S,7S)-7-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	9.9 (36)			
39	(1S,2S,4R,5R,6S,7S)-7-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	0.53 (40)			
40	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-[2-(morpholin-4-yl)pyrimidin-5-yl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (37)			
41	(1S,2S,4R,5R,6S,7S)-7-(2-fluoropyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	24 (121)			
42	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(2-methylpyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	18 (57)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
43	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(5,6-dichloropyridin-3-yl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (168)			
43a	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
43b	(1R,2R,4S,5S,6R,7R)-N-(5,6-dichloropyridin-3-yl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (3)			
44	(1S,2S,4R,5R,6S,7S)-N-(3,4-dichlorophenyl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
45	(1S,2S,4R,5R,6S,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	14 (32)			
46	(1R,2R,4S,5S,6R,7R)-N-(5,6-dichloropyridin-3-yl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			
47	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	7.8 (38)			
47a	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (68)	2.1 (82)	33 (88)	>20 (23)
48	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	22 (80)			
49	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	11 (77)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
49a	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	0.84 (53)			
49b	(1S,2R,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (31)			
50	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[6-(trifluoromethyl)pyridin-2-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	21 (308)			
51	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(pyrimidin-5-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
52	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (4)			
52a	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (96)	0.49 (80)	17 (71)	>20 (36)
52b	(1S,2R,3R,4S,5R)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (1)			
53	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (43)			
53a	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (12)	13 (44)	31 (83)	>20 (0)

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
53b	(1S,2R,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (119)			
54	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (22)			>20 (35)
54a	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	3.5 (45)			>20 (35)
54b	(1S,2R,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (16)			>20 (46)
55	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-[2-(dimethylamino)pyrimidin-5-yl]-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
56	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyrimidin-5-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
57	(1R,2S,3S,4R,5S)-3-(2-aminopyridin-4-yl)-N-(3,4-dichlorophenyl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (56)			
58	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2,5-difluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
59	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2,3-difluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	1.2 (254)			

Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
60	(1R,2S,3S,4R,5S)-3-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (2)			
61	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyrimidin-5-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (24)			
62	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyrimidin-5-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	8.2 (61)			
63	(1R,2S,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-methoxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (9)			
64	(1R,2S,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	21 (253)			
65	(1R,2S,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	18 (169)			
66	(1S,2S,4R,5R,6R,7S)-N-(4-chloro-3-cyanophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	20 (179)			
67	(1S,2S,4R,5R,6R,7S)-N-(4-chloro-2-cyanophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (39)			
68	(1S,2S,4R,5R,6R,7S)-N-(4-chloro-3-fluorophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	15 (306)			

Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
69	(1S,2S,4R,5R,6R,7S)-7-(2-methylpyridin-4-yl)-N-[3-(trifluoromethoxy)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	21 (180)			>20 (63)
70	(1S,2S,4R,5R,6R,7S)-N-(5-methyl-1,3-thiazol-2-yl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (25)			>20 (1)
71	(1S,2S,4R,5R,6R,7S)-N-[3-fluoro-4-(trifluoromethoxy)phenyl]-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	6.2 (250)			
72	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	7.7 (208)			
73	(1R,2R,4S,5S,6S,7R)-N-(5,6-dichloropyridin-3-yl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	16 (127)			
74	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	7.7 (90)			>20 (83)
75	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	4.4 (73)			>20 (45)
76	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2-methoxypyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	5.8 (123)			
77	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (49)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
77a	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (182)	0.69 (120)	3.5 (114)	>20 (45)
77b	(1S,2R,3S,4S,6R)-N-(3,4-dichlorophenyl)-6-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	20 (157)			>20 (47)
77c	(1S,2S,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	13 (72)			3.9 (72)
77d	(1R,2S,3R,4R,6S)-N-(3,4-dichlorophenyl)-6-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	33 (92)			>20 (54)
78	(1R,2R,3S,4R,5S)-N-[3-chloro-4-(2-fluorophenyl)phenyl]-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (70)			
79	(1R,2R,3S,4R,5S)-5-hydroxy-N-(1-methanesulfonylpiperidin-4-yl)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (113)			>20 (34)
80	(1R,2R,3S,4R,5S)-N-(4,5-dichloropyridin-2-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (32)			
81	(1R,2R,3S,4R,5S)-N-(5-chloro-6-methylpyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	2.7 (34)			
82	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyrimidin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (74)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
83	(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (38)	1.5 (150)	12 (106)	>20 (34)
84	(1S,2S,3R,4S,5R)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (61)			>20 (31)
85	(1R,2R,3S,4R,5S)-5-hydroxy-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (56)			
86	(1S,2R,3S,4S,6R)-6-hydroxy-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (38)			
87	(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (14)			
88	(1R,2R,3S,4R,5S)-5-hydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (27)			
89	(1S,2R,3S,4S,6R)-6-hydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
90	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (45)			
90a	(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (101)	2.3 (65)	>50 (98)	>20 (48)

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
90b	(1S,2S,3R,4S,5R)-N-(5,6-dichloropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (44)			>20 (45)
91	(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-3-(2,3-difluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	4.4 (66)			
92	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (57)			
93	(1S,2R,3S,4S,6S)-N-(3,4-dichlorophenyl)-6-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (7)			
94	(1S,2S,3R,4S,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	18 (157)			>20 (0)
95	(1R,2S,3R,4R,6R)-N-(3,4-dichlorophenyl)-6-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	11 (113)			
96	(1R,2R,3S,4R,5R)-5-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	14 (281)			
97	(1R,2R,3S,4R,5R)-5-fluoro-N-(6-methoxypyridin-3-yl)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (2)			
98	(1R,2R,3S,4R,5R)-N-(5,6-dichloropyridin-3-yl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	21 (404)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
99	(1R,2R,3S,4R,5R)-5-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethoxy)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	18 (383)			
100	(1R,2R,3S,4R,5R)-5-fluoro-N-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	18 (310)			
101	(1R,2R,3S,4R,5R)-5-fluoro-N-(1-methyl-1H-pyrazol-3-yl)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	29 (62)			
102	(1R,2R,3S,4R,5R)-5-fluoro-N-(5-methyl-1,3-thiazol-2-yl)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	2.1 (84)			
103	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	24 (153)			10 (79)
104	(1S,2R,3S,4S,6R)-N-(3,4-dichlorophenyl)-6-fluoro-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	14 (96)			
105	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	8.2 (106)			1.7 (68)
106	(1S,2R,3S,4S,6R)-N-(3,4-dichlorophenyl)-6-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	24 (84)			
107	(1R,2R,3S,4R,5S)-5-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	12 (139)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
108	(1S,2R,3S,4S,6R)-6-fluoro-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	27 (137)			
109	(1R,2R,3S,4R,5S)-N-(5,6-dichloropyridin-3-yl)-5-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (164)			
110	(1S,2R,3S,4S,6R)-N-(5,6-dichloropyridin-3-yl)-6-fluoro-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (199)			
111	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-fluoropyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (87)			
112	(1S,2R,3S,4S,6R)-N-(3,4-dichlorophenyl)-6-fluoro-3-(2-fluoropyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (99)			
113	(1R,2R,3S,4R,5S)-3-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-5-fluoro-7-oxabicyclo[2.2.1]heptane-2-carboxamide	30 (103)			
114	(1S,2R,3S,4S,6R)-3-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-6-fluoro-7-oxabicyclo[2.2.1]heptane-2-carboxamide	30 (127)			
115	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-fluoro-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	33 (49)			
116	(1S,2R,3S,4S,6R)-N-(3,4-dichlorophenyl)-6-fluoro-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	23 (58)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
117	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2-methylpyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	3.0 (177)			7.0 (59)
118	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2-methoxypyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	8.2 (118)			
119	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2-fluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	25 (149)			
120	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-[6-(trifluoromethyl)pyridin-2-yl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	20 (102)			4.4 (119)
121	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-7-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	26 (353)			
121a	(1S,2S,4R,5R,6R,7S)-7-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	2.7 (231)			4.5 (80)
121b	(1R,2R,4S,5S,6S,7R)-7-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	22 (92)			
122	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	5.0 (32)			
122a	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	25 (160)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
122b	(1R,2R,4S,5S,6S,7R)-N-(3,4-dichlorophenyl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	17 (217)			
123	(1S,2S,4R,5R,6R,7S)-N-(6-methoxypyridin-3-yl)-7-(6-methylpyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (0)			>20 (48)
124	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(2,3-difluoropyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	2.8 (160)			17 (59)
125	(1S,2S,4R,5R,6R,7S)-N-(6-methoxypyridin-3-yl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	17 (162)			
126	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	10 (212)			
126a	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	5.4 (233)			
126b	(1R,2R,4S,5S,6S,7R)-N-(3,4-dichlorophenyl)-7-(pyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	5.6 (103)			>20 (42)
127	(1S,2S,4R,5R,6R,7S)-7-(2,3-difluoropyridin-4-yl)-N-(6-methoxypyridin-3-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (62)			
128	(1S,2S,4R,5R,6R,7S)-N-(6-methoxypyridin-3-yl)-7-[6-(trifluoromethyl)pyridin-2-yl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	>50 (27)			>20 (39)

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
129	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2-fluoropyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	10 (146)			
130	(1S,2S,4R,5R,6R,7S)-7-(pyrimidin-5-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	10 (237)			
131	(1S,2S,4R,5R,6R,7S)-7-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	19 (360)			
132	(1S,2S,4R,5R,6R,7S)-7-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	18 (321)			
133	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-[2-(morpholin-4-yl)pyrimidin-5-yl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	25 (158)			
134	(1S,2S,4R,5R,6R,7S)-7-(2-fluoropyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	19 (249)			
135	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(2-methylpyrimidin-5-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	16 (237)			
136	(1S,2S,4R,5R,6R,7S)-N-(5,6-dichloropyridin-3-yl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	17 (254)			
137	(1S,2S,4R,5R,6R,7S)-N-(3,4-dichlorophenyl)-7-(pyridin-4-yl)-8-oxatricyclo[3.2.1.0 ^{2,4}]octane-6-carboxamide	21 (202)			
138	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			>20 (24)

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
139	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	21 (223)			
139a	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	25 (275)			1.8 (54)
139b	(1S,2S,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (141)			7.7 (82)
140	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[6-(trifluoromethyl)pyridin-2-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	15 (292)			
141	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(pyrimidin-5-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	13 (43)			
142	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (142)			
142a	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	22 (68)	1.2 (83)	33 (93)	6.6 (81)
142b	(1S,2S,3R,4S,5R)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	0.79 (54)			
143	(1R,2R,3S,4R,5S)-3-(2-aminopyrimidin-5-yl)-N-(3,4-dichlorophenyl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
144	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-[2-(dimethylamino)pyrimidin-5-yl]-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	30 (183)			
145	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	17 (246)			
145a	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide				1.2 (100)
145b	(1S,2S,3R,4S,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-(trifluoromethyl)pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide				11 (83)
146	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2,3-difluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	20 (150)			
147	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2,5-difluoropyridin-4-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	28 (284)			
148	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyrimidin-5-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	7.8 (51)			18 (58)
149	(1R,2R,3S,4R,5S)-3-(2-aminopyridin-4-yl)-N-(3,4-dichlorophenyl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (112)			8.3 (58)
150	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (5)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
151	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-3-(2-fluoropyrimidin-5-yl)-5-hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
152	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(1-methyl-1H-pyrazol-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	12 (44)			2.0 (61)
153	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	19 (121)			>20 (46)
154	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-[2-(trifluoromethyl)pyrimidin-5-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (236)			4.0 (75)
155	(1R,2R,3S,4R,5S)-N-(3,4-dichlorophenyl)-5-methoxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	26 (262)			
156	(1S,2R,3S,4R,5S,6R)-N-(3,4-dichlorophenyl)-5,6-dihydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	18 (28)	0.95 (99)	15 (103)	>20 (42)
157	(1R,2S,3R,4S,5R,6S)-N-(3,4-dichlorophenyl)-5,6-dihydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	29 (57)	2.1 (59)	32 (84)	>20 (15)
158	(1S,2R,3S,4R,5S,6R)-5,6-dihydroxy-3-(2-methylpyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (31)			
159	(1S,2R,3S,4R,5S,6R)-5,6-dihydroxy-3-(pyridin-4-yl)-N-[3-(trifluoromethyl)phenyl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (11)			

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
160	(1S,2R,3S,4R,5S,6R)-N-(3,4-dichlorophenyl)-5,6-dihydroxy-3-(pyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (32)			
161	(1S,2R,3S,4R,5S,6R)-5,6-dihydroxy-3-(2-methylpyridin-4-yl)-N-[2-(trifluoromethyl)pyridin-4-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (29)			
162	(1S,2R,3S,4R,5S,6R)-N-(5,6-dichloropyridin-3-yl)-5,6-dihydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (25)			
163	(1S,2R,3S,4R,5S,6R)-5,6-dihydroxy-N-[6-methyl-5-(trifluoromethyl)pyridin-3-yl]-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (23)			
164	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(6-methylpyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (0)			
165	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-fluoro-3-(2-methoxypyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	6.0 (110)			>20 (59)
166	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-(dimethylamino)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	24 (68)			>20 (0)
167	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-(methylamino)-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	6.9 (83)			
168	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-[(2-hydroxyethyl)amino]-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	0.32 (114)			>20 (0)

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Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
169	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-3-(2-methylpyridin-4-yl)-5-[(oxan-4-yl)amino]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (69)			>20 (54)
170	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-3-(2-methylpyridin-4-yl)-5-[(1r,3r)-3-hydroxycyclobutyl]amino]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (37)			
171	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-(methylamino)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	24 (237)			
172	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-(dimethylamino)-3-(2-fluoropyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	16 (177)			
173	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-3-(2-fluoropyridin-4-yl)-5-[(2-hydroxyethyl)amino]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	27 (54)			
174	(1R,2R,3S,4R,5R)-N-(5,6-dichloropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5-(methylamino)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (37)			
175	(1R,2R,3S,4R,5R)-N-(5,6-dichloropyridin-3-yl)-5-(dimethylamino)-3-(2-fluoropyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	29 (186)			
176	(1R,2R,3S,4R,5R)-N-(5,6-dichloropyridin-3-yl)-3-(2-fluoropyridin-4-yl)-5-[(2-hydroxyethyl)amino]-7-oxabicyclo[2.2.1]heptane-2-carboxamide	25 (51)			

Ex No.		(A) EC ₅₀ μM (% Efficacy)	(B) EC ₅₀ μM (% Efficacy)	(C) IC ₅₀ μM (% Efficacy)	(D) IC ₅₀ μM (% Efficacy)
177	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-3-(2-methylpyridin-4-yl)-5-(morpholin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	22 (211)	1.5 (34)	>50 (33)	1.5 (103)
178	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-5-methyl-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (1)			
179	(1S,2S,3R,4S,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-5-methyl-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	>50 (22)			
180	(1R,2R,3S,4R,5R)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	30 (113)			11 (69)
181	(1S,2S,3R,4S,5S)-N-(3,4-dichlorophenyl)-5-hydroxy-3-(2-methylpyridin-4-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide	27 (243)			>20 (28)

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

TRADUCCIÓN

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

5 (Capítulo II del Tratado de Cooperación en Materia de Patentes)

(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del solicitante o del mandatario: 57749–WO–PCT.

PARA CONTINUAR CON LA TRAMITACIÓN Ver Formulario PCT/IPEA/416.

Solicitud internacional Nro. PCT/IB2018/054123.

10 Fecha de presentación internacional (*día/mes/año*) 07 de junio de 2018.

Fecha de prioridad (*día/mes/año*) 09 de junio de 2017.

Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC:
INV.C07D493/08.

Solicitante: Novartis AG.

15 1. Este informe corresponde al examen preliminar internacional, establecido por esta Autoridad encargada del examen preliminar internacional según el Artículo 35 y se transmite al solicitante de conformidad con el Artículo 36.

2. Este INFORME consiste en un total de 7 hojas, incluida esta carátula.

3. Este informe también contiene ANEXOS, que comprenden:

20 a. ☒ (*remitido al solicitante y a la Oficina Internacional*) un total de 28 hojas, descriptas a continuación:

☒ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas, y/u hojas que contienen rectificaciones autorizadas por esta Administración, a menos que estas hojas hubieran sido reemplazadas o canceladas, y cualquier escrito de acompañamiento (ver Reglas 46.5, 66.8, 70.16, 91.2 y el Artículo 607 de las Instrucciones Administrativas).

☐ hojas que contienen rectificaciones no tomadas en cuenta por esta Administración porque no fueron autorizadas por esta Administración o

notificadas a esta al momento en que esta Administración comenzó a redactar este informe, y cualquier escrito de acompañamiento (Reglas 66.4bis, 70.2(e), 70.16 y 91.2).

5 ☐ hojas de reemplazo y escritos de acompañamiento, que esta Administración considera que, o bien contienen una modificación que se extiende más allá de lo divulgado en la solicitud internacional tal y como fue inicialmente presentada, o bien las hojas de reemplazo no se acompañaron de un escrito indicando la base para la modificación en la solicitud tal y como se presentó, según se indica en el punto 4 del

10 Recuadro I y en el Recuadro Suplementario (ver Regla 70.16.b)).

b.☐ (*remitido únicamente a la Oficina Internacional*) un total de (indicar tipo y número de soporte(s) electrónico(s)) __, que contienen una lista de secuencias, en formato de archivo de texto según Anexo C/ST.25, como se indica en el Recuadro Suplementario relativo a listas de secuencias (ver párrafo 3^{ter} del

15 Anexo C de las Instrucciones Administrativas).

4. El presente informe contiene indicaciones relativas a los puntos siguientes:

- | | |
|--|--|
| ☒ Recuadro I | Base de este informe |
| ☐ Recuadro II | Prioridad |
| ☐ Recuadro III | No formulación de opinión sobre la novedad, la actividad |
| 20 | inventiva y la aplicación industrial |
| ☐ Recuadro IV | Falta de unidad de invención |
| ☒ Recuadro V | Declaración fundamentada según el Artículo 35.2) sobre la |
| | novedad, la actividad inventiva y la aplicación industrial; citas y |
| | explicaciones en apoyo de esta declaración |
| 25 | ☐ Recuadro VI Ciertos documentos citados |
| | ☒ Recuadro VII Defectos en la solicitud internacional |
| | ☒ Recuadro VIII Observaciones relativas a la solicitud internacional |

Fecha de presentación de la petición 09.04.2019

Fecha de finalización del presente informe 18.09.2019

Nombre y dirección postal de la Administración encargada del examen preliminar internacional:

5 Oficina Europea de Patentes

D-80298 Munich

Tel. +49 89 2399 - 0

Fax: +49 89 2399 - 4465

Funcionario autorizado: Kirsch, Cécile

10 Nro. de teléfono: +49 89 2399–2191

Formulario PCT/IPEA/409 (carátula) (enero de 2015)

[En la página siguiente].

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

Solicitud Internacional Nro. PCT/IB2018/054123

15 Recuadro I. Base de este informe

1. Por lo que respecta al idioma, este informe se ha establecido sobre la base:

☒ de la solicitud internacional en el idioma en el cual se presentó

☐ de una traducción de la solicitud internacional al idioma ____, que es el idioma de una traducción proporcionada a los fines de:

20 ☐ búsqueda internacional (según Reglas 12.3.(a) y 23.1.(b))

☐ publicación de la solicitud internacional (según Regla 12.4.(a))

☐ examen preliminar internacional (según Reglas 55.2.(a) y/o 55.3.(a) y (b))

2. En lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se

25 ha establecido sobre la base de *(las hojas de reemplazo que hayan sido enviadas a la Oficina Receptora en respuesta a un requerimiento según el Artículo 14 se las*

denomina en este informe como "inicialmente presentadas" y no se anexan al informe):

La descripción, Páginas

1–121 tal y como fue inicialmente presentada

5 122–146 presentada en formato electrónico el 11–07–2019

Las reivindicaciones, Números

1–23 tal y como fueron inicialmente presentadas

☐ una lista de secuencias – ver Recuadro Suplementario relativo a listas de secuencias.

10 3. ☐ Las modificaciones han ocasionado la anulación de:

☐ la descripción, páginas

☐ las reivindicaciones, números

☐ los dibujos, hojas/figuras

☐ la lista de secuencias (*especificar*):

15 4. ☒ Este informe se ha establecido como si (algunas de) las modificaciones adjuntas a este informe y listadas a continuación no se hubieran realizado dado que, o bien se considera que van más allá de la divulgación tal como se presentó, o bien no se acompañaron con una carta indicando la base para las modificaciones en la solicitud tal y como se presentó, según se indica en
20 el Recuadro Suplementario (Regla 70.2(c) y (c–bis)):

☒ la descripción, páginas 122

☐ las reivindicaciones, números

☐ los dibujos, hojas/figuras

☐ la lista de secuencias (*especificar*):

25 5. ☐ Este informe se ha establecido:

☐ tomando en consideración la **rectificación de un error evidente** autorizado por o notificado a esta Administración según la Regla 91 (Reglas 66.1(d–bis) y 70.2(e)).

5 ☐ sin tomar en consideración la **rectificación de un error evidente** autorizado por o notificado a esta Administración según la Regla 91 (Reglas 66.4bis y 70.2(e)).

Formulario PCT/IPEA/409 (enero de 2015)

[En la página siguiente].

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

10 Solicitud Internacional Nro. PCT/IB2018/054123

6. ☒ En lo que respecta a las búsquedas complementarias (Regla 66.1 ter y 70.2(f)):

☒ esta Administración ha realizado una búsqueda suplementaria el 01.08.2019 (todos los documentos hallados se enumeran en el Casillero

15 Suplementario Relacionado con la Búsqueda Suplementaria).

☐ se han hallado documentos adicionales pertinentes durante la búsqueda suplementaria.

☐ esta Administración no ha realizado búsqueda suplementaria por considerar que no sería de utilidad.

20 7. ☐ El(los) informe(s) de búsqueda internacional suplementario(s) emitido(s) por la(s) Administración(es) ____ ha(n) sido recibido(s) y tomado(s) en consideración para establecer este informe (Regla 45bis.8(b) y (c)).

** Si se utiliza el punto 4, algunas o todas estas páginas pueden marcarse como “sustituida”.*

25 **Recuadro V. Declaración motivada según el Artículo 35(2) con respecto a la novedad, la actividad inventiva o la aplicación industrial; citas y explicaciones en apoyo de esta declaración**

1. Declaración

Novedad (N)

Sí: Reivindicaciones 1–23

No: Reivindicaciones

Actividad inventiva (IS)

Sí: Reivindicaciones 7

5

No: Reivindicaciones 1–6, 8–23

Aplicación industrial (IA)

Sí: Reivindicaciones 1–23

No: Reivindicaciones

2. Citas y explicaciones (Regla 70.7):

ver hoja por separado10 **Recuadro VII Defectos en la solicitud internacional**

Se han comprobado los siguientes defectos en la forma o el contenido de la solicitud internacional:

ver hoja por separado**Recuadro VIII Observaciones relativas a la solicitud internacional**

- 15 Se formulan las siguientes observaciones sobre la claridad de las reivindicaciones, de la descripción y de los dibujos y sobre si las reivindicaciones se fundan totalmente en la descripción:

ver hoja por separado

Formulario PCT/IPEA/409 (enero de 2015)

- 20 *[En la página siguiente].*

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD (HOJA POR SEPARADO)

Solicitud Internacional Nro. PCT/IB2018/054123

Se hace referencia al siguiente documento:

- 25 D1: WO 2015/175487 citado en la solicitud

La presente solicitud está relacionada con derivados de N–ciclil–3–heteroaril–7–oxabicyclo[2.2.1]heptano–2–carboxamida y N–ciclil–7–heteroaril–8–

oxatriciclo[3.2.1.0^{2,4}]octano-6-carboxamida para el tratamiento y la prevención de la artritis y lesiones articulares y para inducir la condrogénesis. También está relacionada con compuestos intermediarios útiles en la preparación de compuestos activos.

5 **Ref. Item I**

Base de este informe

El solicitante ha proporcionado modificaciones solamente para la descripción.

Las modificaciones presentadas introducen materia que se extiende más allá del contenido de la solicitud tal como fue presentada, contrariamente a lo dispuesto en
10 el Artículo 34(2)(b) del PCT.

En la Tabla 1, los compuestos originales 2-30 se han numerado nuevamente como compuestos 3-31, respectivamente.

Sobre la base de los ejemplos 3-31 y la nomenclatura allí divulgada, la numeración en la Tabla 1 se observa como la corrección de un error evidente debido a que la
15 nomenclatura en la Tabla 1 no era consistente con la nomenclatura en los ejemplos correspondientes.

En la Tabla 1, el compuesto original 31 se ha numerado nuevamente como compuesto 31A. Dado que la nomenclatura en la Tabla 1 no correspondía con el ejemplo 31, se permite la nueva numeración ya que no está asociada con ninguna
20 enseñanza nueva.

No obstante, la nueva entrada para el compuesto 2 en la Tabla 1 no está permitida. No existe sustento para los datos biológicos asociados con este compuesto. Al respecto, el solicitante se refiere al documento de prioridad como apoyo para la modificación. Sin embargo, no está permitido añadir a una solicitud internacional
25 materia que solo se encuentra presente en el documento de prioridad de dicha solicitud (GL/PCT-EPO HII, 2.2.4).

Por dichas razones, la modificación propuesta para el ejemplo 2 en la Tabla 1 está

en contravención con los requisitos del Artículo 34(2)(b) del PCT y no está permitida.

Formulario PCT/Separate Sheet/409 (Hoja 1) (EPO–enero 2015)

[En la página siguiente].

5 **INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD (HOJA POR SEPARADO)**

Solicitud Internacional Nro. PCT/IB2018/054123

Ref. Item V

10 **Declaración fundamentada sobre la novedad, la actividad inventiva o la aplicación industrial; citas y explicaciones en apoyo de esta declaración**

Las reivindicaciones 19–23 se relacionan con materia que esta Administración considera alcanzada por las disposiciones de la Regla 39.1(iv) / 67.1(iv) del PCT.

La patentabilidad puede depender de la formulación de las reivindicaciones. La EPO [*Oficina Europea de Patentes, por sus siglas en inglés*], por ejemplo, no
15 reconoce como patentables las reivindicaciones del uso de un compuesto en un tratamiento médico, pero puede permitir reivindicaciones de un producto, en particular sustancias o composiciones para usar en un primer tratamiento médico o en un tratamiento adicional.

Se ha evaluado la patentabilidad, en particular la novedad y la actividad inventiva
20 de las reivindicaciones 19–23 sobre la base de un producto con propósitos limitados tomando en consideración los presuntos efectos de los compuestos.

1. Novedad, Artículo 33(2) del PCT

El documento D1 divulga derivados de 7-oxabicyclo[2.2.1]heptano–2–carboxamida y su uso para el tratamiento de la artritis o las lesiones articulares. La materia de
25 D1 se ha suprimido mediante dos exclusiones (R6 y R7 de D1 son H o alquilo). Los compuestos activos, las composiciones farmacéuticas y los usos médicos también son novedosos. Dado que las exclusiones también se aplican a los compuestos

intermediarios, estos intermediarios también son novedosos con respecto a D1.

Se reconoce la novedad frente a D1.

2. Actividad inventiva, Artículo 33(3) del PCT

2.1. El documento D1 representa la técnica conocida más cercana. Los compuestos
5 de D1 difieren de la materia reivindicada debido a la combinación de sustituyentes en las posiciones 5 y 6.

2.2 El efecto asociado con esta diferencia es la conservación de las propiedades biológicas.

El problema a resolver por la presente solicitud se observa en la provisión de
10 derivados de 7-oxabicyclo[2.2.1]heptano-2-carboxamida adicionales para usar en el tratamiento de la artritis y las lesiones articulares.

De acuerdo con la Tabla 3, no todos los compuestos son activos (el porcentaje de eficacia de una cantidad de compuestos es 0 o próximo a 0). Por lo tanto, es evidente que la materia reivindicada no ha sido resuelta en la totalidad del alcance
15 reivindicado.

Formulario PCT/Separate Sheet/409 (Hoja 2) (EPO-enero 2015)

[En la página siguiente].

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD (HOJA POR SEPARADO)

20 Solicitud Internacional Nro. PCT/IB2018/054123

2.3. A partir de D1 resulta evidente que los compuestos excluidos de la fórmula I exhiben la actividad reivindicada. La jurisprudencia establece que si se puede emplear una exclusión para hacer novedosa la enseñanza de una invención, esta no puede hacer que una enseñanza obvia resulte inventiva.

25 En este caso, la estructura de los compuestos reivindicados está estrechamente ligada con la de los compuestos de D1. En el campo farmacéutico, la motivación para elaborar nuevos compuestos deriva de la expectativa de que compuestos con

estructuras similares tengan una actividad similar. Por lo tanto, el experto en la técnica estaría motivado para preparar productos relacionados con la técnica conocida para arribar a los productos reivindicados en la presente con la expectativa de obtener productos con beneficios adicionales, los cuales serían
5 útiles para tratar la artritis y las lesiones articulares.

Por lo tanto, los compuestos reivindicados son meramente alternativas obvias de los compuestos activos divulgados en el documento D1. Por lo tanto, la materia reivindicada carece de actividad inventiva.

2.4. La quiralidad de las reivindicaciones 2 y 3 ya fue divulgada en la reivindicación
10 10 de D1. De acuerdo con las reivindicaciones 4 a 6, las realizaciones preferidas en las posiciones 4 y 6 tienen átomos de hidrógeno en estas posiciones lo cual se acerca mucho a los compuestos de D1. De acuerdo con las reivindicaciones 4–5 y 11–13 de D1 se prefieren las realizaciones de las reivindicaciones 8 a 9. Las realizaciones de las reivindicaciones 10 y 11 corresponden a las enseñanzas de las
15 reivindicaciones 6–7 y 14–15 de D1. Los compuestos específicos de la reivindicación 12 también están estrechamente relacionados con los compuestos a modo de ejemplo de D1. Los hidratos, como en la reivindicación 13, ya se enseñaron en D1, ver página 40, último párrafo, hasta página 41, primer párrafo. El compuesto intermediario de acuerdo con las reivindicaciones se emplea del mismo
20 modo en D1, ver, por ejemplo, la Fórmula 2a y los ejemplos sintéticos. Las composiciones farmacéuticas y los usos médicos se divulgan en las reivindicaciones 17, 20 y 23–25 y también carecen de actividad inventiva. Las combinaciones se divulgan en la página 59, penúltimo párrafo de D1.

2.5. La materia de la reivindicación 7 donde los átomos de carbono en las
25 posiciones 5 y 6 están enlazados para formar un ciclopropilo no se torna obvia a partir de las enseñanzas de D1 y se considera inventiva para aquellos compuestos que resuelven fehacientemente el problema planteado.

Ref. Item VII**Defectos en la solicitud internacional**

En la descripción se deberá eliminar la expresión “incorporado a la presente a modo de referencia” como así también cualquier expresión similar.

- 5 Formulario PCT/Separate Sheet/409 (Hoja 3) (EPO–enero 2015)

[En la página siguiente].

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD (HOJA POR SEPARADO)

Solicitud Internacional Nro. PCT/IB2018/054123

10 **Ref. Item VIII**

Observaciones relativas a la solicitud internacional

1. La reivindicación 12 contiene referencias a la descripción. De acuerdo con la Regla 6.2(a) del PCT, las reivindicaciones no deberán contener tales referencias excepto cuando fuera absolutamente necesario, lo cual no es el caso en la
15 presente.

2. La materia descrita en la página 17, realización 29, compuestos 5to. y 11mo. (insaturación en el anillo) no está comprendida por el alcance de las reivindicaciones. Esta inconsistencia entre las reivindicaciones y la descripción lleva a dudar acerca de la materia que se busca proteger, por lo cual las reivindicaciones
20 se vuelven confusas, Artículo 6 del PCT.

3. La declaración vaga e imprecisa de la descripción en la página 146, último párrafo, implica que la materia que se busca proteger puede ser diferente a la definida en las reivindicaciones, lo cual da por resultado falta de claridad (Artículo 6 del PCT) cuando se usa para interpretarlas.
- 25 4. Un compuesto “para la reparación de cartílagos” (ver segunda parte de la reivindicación 17) se interpreta como que se refiere a un compuesto adecuado para

dicho uso y no es una limitación sobre el compuesto. Por lo tanto, dicha redacción parecería redundante frente a la reivindicación 1.

5. Los compuestos 3 y 31A son iguales (el mismo nombre químico). No obstante, los datos biológicos difieren en la Tabla 1. La consecuencia es falta de claridad.

- 5 Formulario PCT/Separate Sheet/409 (Hoja 4) (EPO–enero 2015)

[En la página siguiente].

PAT057749–WO–PCT

En relación con: Novartis AG

Solicitud Nro.: PCT/IB2018/054123

- 10 Fecha de presentación internacional: 07 de junio de 2018.

Para: COMPUESTOS Y COMPOSICIONES PARA INDUCIR CONDRÓGENESIS

**RESPUESTA AL DICTAMEN POR ESCRITO DE LA AUTORIDAD ENCARGADA
DEL EXAMEN PRELIMINAR INTERNACIONAL**

Oficina Europea de Patentes

- 15 D–80298 Munich

Atención: Cécile Kirsch

De nuestra consideración:

- El solicitante presenta esta respuesta al Dictamen por Escrito de la Autoridad Encargada del Examen Preliminar Internacional (IPEA) con fecha 17 de mayo de 2019. La IPEA indicó que “[s]obre la base de los ejemplos 4–30 y la nomenclatura allí divulgada, la nueva numeración en la Tabla 1 se observa como la corrección de un error evidente”. La IPEA también indicó que la “nueva numeración de 31 a 2, y de 2 y 3 a 3 y 4 respectivamente no deriva evidentemente *[sic]* de la solicitud tal como fue presentada”.

- 25 El nuevo Ejemplo Nro. 2 y los datos sobre la actividad asociada están sustentados por el Ejemplo Nro. 2 en la Tabla 3 de la solicitud provisional de los EE.UU. con Nro. de Acta 62/517.394 presentada el 9 de junio de 2017. La nomenclatura en el

nuevo Ejemplo Nro. 2 también está de acuerdo con la nomenclatura en el Ejemplo 2 correspondiente del documento de prioridad. Asimismo, los Ejemplos nuevamente numerados Nro. 3 y 4 (anteriormente Ejemplos Nro. 2 y 3) están sustentados por los Ejemplos 3 y 4 correspondientes y la nomenclatura allí divulgada.

Para mayor claridad y para corregir errores de numeración evidentes, los Ejemplos Nro. 4–30 tal como fueron originalmente presentados se numeraron nuevamente como Ejemplos Nro. 5–31, respectivamente. La modificación está sustentada por la nomenclatura en los Ejemplos 5–31 correspondientes. El Ejemplo Nro. 31 tal como fue originalmente presentado ha sido numerado nuevamente como Ejemplo Nro. 31A, para evitar la numeración duplicada.

Sobre la base de lo expuesto, el Solicitante respetuosamente solicita que la IPEA modifique la solicitud reemplazando las páginas 122–146 de la descripción con las hojas de reemplazo en el Apéndice A. Las hojas de reemplazo corrigen errores tipográficos evidentes y no contienen una materia nueva:

- Se ha agregado el nuevo Ejemplo Nro. 2, de acuerdo con el Ejemplo Nro. 2 en la Tabla 3 del documento de prioridad;
- Los Ejemplos 2 y 3 tal como se presentaron originalmente se han numerado nuevamente como Ejemplos Nro. 3 y 4, respectivamente, de acuerdo con los Ejemplos 3 y 4 correspondientes;

1

[En la página siguiente].

PAT057749–WO–PCT

- Los Ejemplos Nro. 4–30 tal como fueron originalmente presentados se han numerado nuevamente como Ejemplos Nro. 5–31, respectivamente, de acuerdo con los Ejemplos 5–31 correspondientes;

- El Ejemplo Nro. 31 tal como fue originalmente presentado se ha numerado nuevamente como Ejemplo Nro. 31A, para distinguirlo del Ejemplo Nro. 31 nuevamente numerado (originalmente Ejemplo Nro. 30);
- Se añadió “*rac*–” antes de los nombres de los compuestos en los Ejemplos Nro. 2, 11, 12, 24, 43, 47, 49, 52, 53, 54, 77, 90, 121, 122, 126, 139 y 142, de acuerdo con los ejemplos correspondientes.

Atentamente,

/Emily T. Wu/

Emily T. Wu

10 Nro. de registro 46.473

Fecha: 11 de julio de 2019

Cliente Nro. 29490

The Genomics Institute of the

Novartis Research Foundation (GNF)

15 Oficina: (858) 812–1539

2

[En la página siguiente].

PAT057749–WO–PCT

APÉNDICE A

20 **Hojas de reemplazo 122–146**

[En la página siguiente].

PCT/IB 2018/054 123 – 11.07.2019

PAT057749–WO–PCT

Tinción con fosfatasa alcalina y cuantificación en C3H10T1/2

25 Para iniciar la diferenciación en C3H10T1/2, Clon 8 (nro. de cat. ATCC CCL–226), se plaquearon 4.000 células por pocillo en una placa CellCarrier Ultra 384 Perkin Elmer en DMEM/alta glucosa (nro. de cat. HyClone SH30022.01) que contenía FBS

10% y antibiótico/antimicótico 1x (HyClone nro. de cat. SV30079.01). Luego de 24 horas se añadió el compuesto de ensayo en cada pocillo en la dosis indicada. Los cultivos se dejaron crecer a 37°C durante 6 días.

Para detectar la presencia de células hipertróficas, se fijaron C3H10T1/2 con paraformaldehído 4% y colorante Hoeschst durante 20 minutos, se lavaron en PBS, luego se tiñeron con sal RR Azul para tinción rápida con solución alcalina naftol AS–MX fosfato. Cuando se observó que las células se volvían azules, luego de aproximadamente 3 horas a 37°C, se lavaron seis veces con PBS.

Se tomaron imágenes de la tinción con ALP (fosfatasa alcalina) mediante microscopia fluorescente, usando la longitud de onda 561, y/o se cuantificó por alto contenido tomando imágenes con un microscopio confocal ImageXpress (Molecular Devices, Sunnyvale, CA). Se analizaron los datos con la aplicación personalizada de puntaje celular con longitud de onda múltiple observando la cantidad de células ALP positivas por pocillo.

15 Ensayo y cuantificación de movilización de calcio

Se plaquearon NHAC en una placa Greiner 1536 a razón de 2000 células/pocillo en un volumen de 4ul. Luego de 24 horas, se añadieron 4ul de solución para tinción calcio 5 (solución salina equilibrada de Hank/tampón HEPES que contenía 5mM de Probenecid) y se incubaron durante 1 hora a temperatura ambiente. Se realizaron lecturas de fluorescencia con una longitud de onda de excitación de 470–495nm y una longitud de onda de emisión de 515–575nm empleando un sistema de detección de alto rendimiento FLIPR (Molecular Devices, Sunnyvale, CA). Luego se añadió a cada pocillo el compuesto de ensayo en la dosis indicada. Se midió la señal antes y después de dispensar el compuesto usando un primer intervalo de 1 segundo para 60 lecturas y un segundo intervalo de 3 segundos para 20 lecturas. Los datos se analizaron con el software ScreenWorks® de Molecular Devices.

La actividad de los compuestos de la presente invención en los siguientes ensayos se resume en la Tabla 3. Leyenda: (A) ensayo de movilización de calcio; (B) ensayo de colágeno Tipo II; (C) ensayo de fosfatasa alcalina en NHAC; y (D) ensayo de fosfatasa alcalina en C3H10T1/2.

5

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
1	(1S,2S,4R,5R,6S,7S) -N-(5,6-dicloropiridin-3-il)-7-(2-metoxipiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	3,4 (164)			
2	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(6-metoxipiridin-3-il)-7-(6-metilpiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (0)			

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Hoja modificada

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Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
3	(1S,2S,4R,5R,6S,7S)-N-(6-metoxipiridin-3-il)-7-(6-metilpiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	0,30 (45)			
4	(1R,2R,4S,5S,6R,7R)-N-(6-metoxipiridin-3-il)-7-(6-metilpiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (0)			
5	(1 R,2S,3S,4R,5S)-N-(4,5-dicloropiridin-2-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-	>50 (28)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
	oxabicyclo[2.2.1]heptano-2-carboxamida				
6	(1R,2S,3S,4R,5S)-N-(5-cloro-6-metilpiridin-3-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (18)			
7	(1R,2S,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (17)			
8	(1S,2R,3R,4S,5R)-N-(5,6-dicloropiridin-3-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
9	(1R,2S,3S,4R,5S)-5-hidroxi-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (50)		>31 (62)	>20 (16)
10	(1S,2S,3S,4S,6R)-6-hidroxi-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
11	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-5-hidroxi-3-(piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
11a	(1R,2S,3S,4R,5S)-N-(5,6-Dicloropiridin-3-il)-5-hidroxi-3-(piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (55)			
12	<i>rac</i> -(1R,2S,3S,4R,5S)-5-hidroxi-3-(piridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (27)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
12a	(1R,2S,3S,4R,5S)-5-hidroxi-3-(piridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	0,27 (98)	2.9 (91)	48 (65)	>20 (6)
13	(1S,2S,3S,4S,6R)-6-hidroxi-3-(piridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (22)			
14	(1R,2S,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	4,5 (68)			
15	(1R,2S,3S,4R,5R)-5-fluoro-N-(6-metoxipiridin-3-il)-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	8,3 (115)			
16	(1R,2S,3S,4R,5R)-5-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
17	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	21 (105)			
18	(1R,2S,3S,4R,5S)-5-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
19	(1R,2S,3S,4R,5S)-N-(5,6-Dicloropiridin-3-il)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
20	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metoxipiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	25 (258)			
21	(1R,2S,3S,4R,5S)-3-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-5-fluoro-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (5)			
22	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(6-metilpiridin-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	27 (159)			
23	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-fluoropiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	4,2 (128)			
24	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(3,4-diclorofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (54)			
24a	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclorofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	6,1 (99)	0,78 (29)	30 (100)	>20 (28)
24b	(1R,2R,4S,5S,6R,7R)-N-(3,4-diclorofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (0)			
25	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclorofenil)-7-(2-metoxipiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	11 (71)			
26	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclorofenil)-7-(2-fluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	17 (52)			
27	(1S,2S,4R,5R,6S,7S)-7-(2-Metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-8-	23 (54)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
	oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida				
28	(1S,2S,4R,5R,6S,7S)-N- (3,4- diclorofenil)-7-(pirimidin-5- il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	13 (120)		34 (71)	>20 (48)
29	(1R,2R,4S,5S,6R,7R)-N- (3,4- diclorofenil)-7-(pirimidin-5- il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano- 6- carboxamida	23 (167)			
30	(1S,2S,4R,5R,6S,7S)-N-(3,4- diclorofenil)-7-(2,3- difluoropiridin-4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano- 6- carboxamida	>50 (6)			
31	(1R,2R,4S,5S,6R,7R)-N-(3,4- diclorofenil)-7-(2,3- difluoropiridin-4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	10 (133)			
31A	(1S,2S,4R,5R,6S,7S)-N-(6- metoxipiridin-3-il)-7-(6- metilpiridin-3-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	>50 (0)			
32	(1S,2S,4R,5R,6S,7S)-N-(5,6- Dicloropiridin-3-il)-7-(2,3- difluoropiridin-4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	13 (143)			
33	(1S,2S,4R,5R,6S,7S)-N-(6- Metoxipiridin-3-il)-7- (piridin- 4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	4,6 (49)			
34	(1S,2S,4R,5R,6S,7S)-7-(2,3- Difluoropiridin-4-il)-N-(6- metoxipiridin-3-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	>50 (3)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
35	(1S,2S,4R,5R,6S,7S)-N-(6-Metoxipiridin-3-il)-7-[6-(trifluorometil)piridin-2-il]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (0)			
36	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclororenil)-7-(2-fluoropirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	8,6 (124)			
37	(1S,2S,4R,5R,6S,7S)-7-(pirimidin-5-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (26)			
38	(1S,2S,4R,5R,6S,7S)-7-(piridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	9,9 (36)			
39	(1S,2S,4R,5R,6S,7S)-7-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	0,53 (40)			
40	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclorofenil)-7-[2-(morfolin-4-il)pirimidin-5-il]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (37)			
41	(1S,2S,4R,5R,6S,7S)-7-(2-Fluoropiridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	24 (121)			
42	(1S,2S,4R,5R,6S,7S)-N-(3,4-diclororenil)-7-(2-metilpirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	18 (57)			
43	<i>rac</i> -(1S,2S,4R,5R,6S,7S)-N-(5,6-dicloropiridin-3-il)-7-(piridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (168)			
43a	(1S,2S,4R,5R,6S,7S)-N-(3,4-	>50 (0)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
	diclorofenil)-7-(piridin-4-il)- 8-oxatriciclo[3.2.1.0 2,4]octano-6-carboxamida				
43b	(1R,2R,4S,5S,6R,7R)-N-(5,6- dicloropiridin-3-il)-7-(piridin- 4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	>50 (3)			
44	(1S,2S,4R,5R,6S,7S)-N-(3,4- diclorofenil)-7-(piridin-4-il)- 8-oxatriciclo[3.2.1.0 2,4]octano-6-carboxamida	>50 (0)			
45	(1S,2S,4R,5R,6S,7S)-N-(5,6- dicloropiridin-3-il)-7-(2- metilpiridin-4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	14 (32)			
46	(1R,2R,4S,5S,6R,7R)-N-(5,6- dicloropiridin-3-il)-7-(2- metilpiridin-4-il)-8- oxatriciclo[3.2.1.0 ^{2,4}]octano-6- carboxamida	>50 (0)			
47	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4- diclorofenil)-5-hidroxi-3-(piridin-4-il)-7- oxabicyclo[2.2.1]heptano-2- carboxamida	7,8 (38)			
47a	(1R,2S,3S,4R,5S)-N-(3,4- diclorofenil)-5-hidroxi-3-(piridin- 4-il)-7-oxabicyclo[2.2.1]heptano- 2-carboxamida	>50 (68)	2,1 (82)	33 (88)	>20 (23)
48	(1R,2S,3S,4R,5S)-N-(3,4- diclorofenil)-5-hidroxi-3-(6- metilpiridin-3-il)-7- oxabicyclo[2.2.1]heptano-2- carboxamida	22 (80)			
49	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4- diclorofenil)-5-hidroxi-3-(2- metoxipiridin-4-il)-7- oxabicyclo[2.2.1]heptano-2- carboxamida	11 (77)			
49a	(1R,2S,3S,4R,5S)-N-(3,4- diclorofenil)-5-hidroxi-3-(2- metoxipiridin-4-il)-7-	0,84 (53)			

Ej. Nro.		(A) EC ₅₀ µM (% eficacia)	(B) EC ₅₀ µM (% eficacia)	(C) IC ₅₀ µM (% eficacia)	(D) IC ₅₀ µM (% eficacia)
	oxabíciclo[2.2.1]heptano-2-carboxamida				
49b	(1S,2R,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metoxipiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (31)			
50	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[6-(trifluorometil)piridin-2-il]-7-oxabíciclo[2.2.1]heptano-2-carboxamida	21 (308)			
51	(1R,2S,3S,4R,5S)-N-(3,4-diclororenil)-5-hidroxi-3-(pirimidin-5-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (0)			
52	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (4)			
52a	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (96)	0,49 (80)	17 (71)	>20 (36)
52b	(1S,2R,3R,4S,5R)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (1)			
53	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (43)			
53a	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (12)	13 (44)	31 (83)	>20 (0)
53b	(1S,2R,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-	>50 (119)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
	oxabicyclo[2.2.1]heptano-2-carboxamida				
54	<i>rac</i> -(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (22)			>20 (35)
54a	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	3,5 (45)			>20 (35)
54b	(1S,2R,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (16)			>20 (46)
55	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-[2-(dimetilamino)pirimidin-5-il]-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
56	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpirimidin-5-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
57	(1R,2S,3S,4R,5S)-3-(2-aminopiridin-4-il)-N-(3,4-diclorofenil)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (56)			
58	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2,5-difluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
59	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2,3-difluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	1,2 (254)			
	(1R,2S,3S,4R,5S)-3-(2-aminopirimidin-5-il)-N-(3,4-				

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
60	diclorofenil)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (2)			
61	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropirimidin-5-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (24)			
62	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)pirimidin-5-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	8,2 (61)			
63	(1R,2S,3S,4R,5S)-N-(3,4-diclorofenil)-5-metoxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (9)			
64	(1R,2S,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(6-metilpiridin-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	21 (253)			
65	(1R,2S,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metoxipiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	18 (169)			
66	(1S,2S,4R,5R,6R,7S)-N-(4-cloro-3-cianofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	20 (179)			
67	(1S,2S,4R,5R,6R,7S)-N-(4-cloro-2-cianofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (39)			
68	(1S,2S,4R,5R,6R,7S)-N-(4-cloro-3-fluorofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	15 (306)			
69	(1S,2S,4R,5R,6R,7S)-7-(2-Metilpiridin-4-il)-N-[3-	21 (180)			>20 (63)

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
	(trifluorometoxi)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida				
70	(1S,2S,4R,5R,6R,7S)-N-(5-Metil-1,3-tiazol-2-il)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (25)			>20 (1)
71	(1S,2S,4R,5R,6R,7S)-N-[3-fluoro-4-(trifluorometoxi)fenil]-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	6,2 (250)			
72	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	7,7 (208)			
73	(1R,2R,4S,5S,6S,7R)-N-(5,6-Dicloropiridin-3-il)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	16 (127)			
74	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(6-metilpiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	7,7 (90)			>20 (83)
75	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(pirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	4,4 (73)			>20 (45)
76	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(2-metoxipiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	5,8 (123)			
77	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	26 (49)			
	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-				

Ej. Nro.		(A) EC ₅₀ µM (% eficacia)	(B) EC ₅₀ µM (% eficacia)	(C) IC ₅₀ µM (% eficacia)	(D) IC ₅₀ µM (% eficacia)
77a	oxabíciclo[2.2.1]heptano-2-carboxamida	26 (182)	0,69 (120)	3,5 (114)	>20 (45)
77b	(1S,2R,3S,4S,6R)-N-(3,4-diclorofenil)-6-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	20 (157)			>20 (47)
77c	(1S,2S,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	13 (72)			3,9 (72)
77d	(1R,2S,3R,4R,6S)-N-(3,4-diclorofenil)-6-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	33 (92)			>20 (54)
78	(1R,2R,3S,4R,5S)-N-[3-cloro-4-(2-fluorofenil)fenil]-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (70)			
79	(1R,2R,3S,4R,5S)-5-hidroxi-N-(1-metanosulfonilpiperidin-4-il)-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (113)			>20 (34)
80	(1R,2R,3S,4R,5S)-N-(4,5-Dicloropiridin-2-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (32)			
81	(1R,2R,3S,4R,5S)-N-(5-cloro-6-metilpiridin-3-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	2,7 (34)			
82	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpirimidin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (74)			
	(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-5-hidroxi-3-				

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
83	(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (38)	1,5 (150)	12 (106)	>20 (34)
84	(1S,2S,3R,4S,5R)-N-(5,6-dicloropiridin-3-il)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (61)			>20 (31)
85	(1R,2R,3S,4R,5S)-5-hidroxi-3-(2-metilpiridin-4-il)-N-[3- (trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (56)			
86	(1S,2R,3S,4S,6R)-6-hidroxi-3-(2-metilpiridin-4-il)-N-[3- (trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (38)			
87	(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-5-hidroxi- 3-(piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (14)			
88	(1R,2R,3S,4R,5S)-5-hidroxi-3-(piridin-4-il)-N-[3- (trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (27)			
89	(1S,2R,3S,4S,6R)-6-hidroxi-3-(piridin-4-il)-N-[3- (trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50(0)			
90	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-3-(2-fluoropiridin-4-il)-5-hidroxi-7- oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (45)			
90a	(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (101)	2,3 (65)	>50 (98)	>20 (48)

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
90b	(1S,2S,3R,4S,5R)-N-(5,6-dicloropiridin-3-il)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (44)			>20 (45)
91	(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-3-(2,3-difluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	4,4 (66)			
92	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (57)			
93	(1S,2R,3S,4S,6S)-N-(3,4-diclorofenil)-6-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (7)			
94	(1S,2S,3R,4S,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	18 (157)			>20 (0)
95	(1R,2S,3R,4R,6R)-N-(3,4-diclorofenil)-6-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	11 (113)			
96	(1R,2R,3S,4R,5R)-5-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-	14 (281)			
97	(1R,2R,3S,4R,5R)-5-fluoro-N-(6-metoxipiridin-3-il)-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-	>50 (2)			
98	(1R,2R,3S,4R,5R)-N-(5,6-dicloropiridin-3-il)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	21 (404)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
99	(1R,2R,3S,4R,5R)-5-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometoxi)fenil]-7-oxabicyclo[2.2.1]heptano-	18 (383)			
100	(1R,2R,3S,4R,5R)-5-fluoro-N-[3-fluoro-4-(trifluorometoxi)fenil]-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-	18 (310)			
101	(1R,2R,3S,4R,5R)-5-fluoro-N-(1-metil-1 H-pirazol-3-il)-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-	29 (62)			
102	(1R,2R,3S,4R,5R)-5-fluoro-N-(5-metil-1,3-tiazol-2-il)-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-	2,1 (84)			
103	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metoxipiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	24 (153)			10 (79)
104	(1S,2R,3S,4S,6R)-N-(3,4-diclorofenil)-6-fluoro-3-(2-metoxipiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	14 (96)			
105	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	8,2 (106)			1,7 (68)
106	(1S,2R,3S,4S,6R)-N-(3,4-diclorofenil)-6-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	24 (84)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
107	(1R,2R,3S,4R,5S)-5-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-	12 (139)			
108	(1S,2R,3S,4S,6R)-6-fluoro-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-	27 (137)			
109	(1R,2R,3S,4R,5S)-N-(5,6-dicloropiridin-3-il)-5-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	28 (164)			
110	(1S,2R,3S,4S,6R)-N-(5,6-dicloropiridin-3-il)-6-fluoro-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	28 (199)			
111	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(2-fluoropiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	28 (87)			
112	(1S,2R,3S,4S,6R)-N-(3,4-diclorofenil)-6-fluoro-3-(2-fluoropiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	28 (99)			
113	(1R,2R,3S,4R,5S)-3-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-5-fluoro-7-oxabicyclo[2.2.1]heptano-2-carboxamida	30 (103)			
114	(1S,2R,3S,4S,6R)-3-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-6-fluoro-7-oxabicyclo[2.2.1]heptano-2-carboxamida	30 (127)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
115	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-fluoro-3-(6- metilpiridin-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	33 (49)			
116	(1S,2R,3S,4S,6R)-N-(3,4-diclorofenil)-6-fluoro-3-(6- metilpiridin-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	23 (58)			
117	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2-metilpiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	3,0 (177)			7,0 (59)
118	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2-metoxipiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	8,2 (118)			
119	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2-fluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	25 (149)			
120	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-[6-(trifluorometil)piridin-2-il]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	20 (102)			4,4 (119)
121	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-7-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	26 (353)			
121a	(1S,2S,4R,5R,6R,7S)-7-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	2,7 (231)			4,5 (80)
121b	(1R,2R,4S,5S,6S,7R)-7-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	22 (92)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
122	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	5,0 (32)			
122a	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	25 (160)			
122b	(1R,2R,4S,5S,6S,7R)-N-(3,4-diclorofenil)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	17 (217)			
123	(1S,2S,4R,5R,6R,7S)-N-(6-metoxipiridin-3-il)-7-(6-metilpiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50(0)			>20 (48)
124	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(2,3-difluoropiridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	2,8 (160)			17 (59)
125	(1S,2S,4R,5R,6R,7S)-N-(6-metoxipiridin-3-il)-7-(piridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	17 (162)			
126	<i>rac</i> -(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(pirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	10 (212)			
126a	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(pirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	5,4 (233)			
126b	(1R,2R,4S,5S,6S,7R)-N-(3,4-diclorofenil)-7-(pirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	5,6 (103)			>20 (42)

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
127	(1S,2S,4R,5R,6R,7S)-7-(2,3-difluoropiridin-4-il)-N-(6-metoxipiridin-3-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (62)			
128	(1S,2S,4R,5R,6R,7S)-N-(6-metoxipiridin-3-il)-7-[6-(trifluorometil)piridin-2-il]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	>50 (27)			>20 (39)
129	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2-fluoropirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	10 (146)			
130	(1S,2S,4R,5R,6R,7S)-7-(pirimidin-5-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	10 (237)			
131	(1S,2S,4R,5R,6R,7S)-7-(piridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	19 (360)			
132	(1S,2S,4R,5R,6R,7S)-7-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	18 (321)			
133	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-[2-(morfolin-4-il)pirimidin-5-il]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	25 (158)			
134	(1S,2S,4R,5R,6R,7S)-7-(2-fluoropiridin-4-il)-N-[3-(trifluorometil)fenil]-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	19 (249)			
135	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(2-metilpirimidin-5-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	16 (237)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
136	(1S,2S,4R,5R,6R,7S)-N-(5,6-dicloropiridin-3-il)-7-(piridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	17 (254)			
137	(1S,2S,4R,5R,6R,7S)-N-(3,4-diclorofenil)-7-(piridin-4-il)-8-oxatriciclo[3.2.1.0 ^{2,4}]octano-6-carboxamida	21 (202)			
138	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(6-metilpiridin-3-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	>50 (0)			>20 (24)
139	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metoxipiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	21 (223)			
139a	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metoxipiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	25 (275)			1,8 (54)
139b	(1S,2S,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metoxipiridin-4-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	26 (141)			7,7 (82)
140	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[6-(trifluorometil)piridin-2-il]-7-oxabíciclo[2.2.1]heptano-2-carboxamida	15 (292)			
141	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(pirimidin-5-il)-7-oxabíciclo[2.2.1]heptano-2-carboxamida	13 (43)			
142	<i>rac</i> -(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabíciclo[2.2.1]heptano-2-carboxamida	28 (142)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
142a	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	22 (68)	1,2 (83)	33 (93)	6,6 (81)
142b	(1S,2S,3R,4S,5R)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	0,79 (54)			
143	(1R,2R,3S,4R,5S)-3-(2-aminopirimidin-5-il)-N-(3,4-diclorofenil)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
144	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-[2-(dimetilamino)pirimidin-5-il]-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	30 (183)			
145	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	17 (246)			
145a	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida				1,2 (100)
145b	(1S,2S,3R,4S,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-(trifluorometil)piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida				11 (83)
146	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2,3-difluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	20 (150)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
147	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2,5-difluoropiridin-4-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-carboxamida	28 (284)			
148	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpirimidin-5-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	7,8 (51)			18 (58)
149	(1R,2R,3S,4R,5S)-3-(2-aminopiridin-4-il)-N-(3,4-diclorofenil)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-	26 (112)			8,3 (58)
150	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (5)			
151	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-3-(2-fluoropirimidin-5-il)-5-hidroxi-7-oxabicyclo[2.2.1]heptano-2-	>50 (0)			
152	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(1-metil-1 H-pirazol-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	12 (44)			2,0 (61)
153	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(1-metil-1 H-pirazol-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	19 (121)			>20 (46)
154	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-[2-(trifluorometil)pirimidin-5-il]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	26 (236)			4,0 (75)
155	(1R,2R,3S,4R,5S)-N-(3,4-diclorofenil)-5-metoxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	26 (262)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
156	(1S,2R,3S,4R,5S,6R)-N-(3,4-diclorofenil)-5,6-dihidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	18 (28)	0,95 (99)	15 (103)	>20 (42)
157	(1R,2S,3R,4S,5R,6S)-N-(3,4-diclorofenil)-5,6-dihidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	29 (57)	2,1 (59)	32 (84)	>20 (15)
158	(1S,2R,3S,4R,5S,6R)-5,6-dihidroxi-3-(2-metilpiridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-	>50 (31)			
159	(1S,2R,3S,4R,5S,6R)-5,6-dihidroxi-3-(piridin-4-il)-N-[3-(trifluorometil)fenil]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (11)			
160	(1S,2R,3S,4R,5S,6R)-N-(3,4-diclorofenil)-5,6-dihidroxi-3-(piridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (32)			
161	(1S,2R,3S,4R,5S,6R)-5,6-dihidroxi-3-(2-metilpiridin-4-il)-N-[2-(trifluorometil)piridin-4-il]-7-oxabicyclo[2.2.1]heptano-2-	>50 (29)			
162	(1S,2R,3S,4R,5S,6R)-N-(5,6-dicloropiridin-3-il)-5,6-dihidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (25)			
163	(1S,2R,3S,4R,5S,6R)-5,6-dihidroxi-N-[6-metil-5-(trifluorometil)piridin-3-il]-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (23)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
164	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(6- metilpiridin-3-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (0)			
165	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-fluoro-3-(2- metoxipiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	6,0 (110)			>20 (59)
166	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-(dimetilamino)-3-(2- metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	24 (68)			>20 (0)
167	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-(metilamino)-3-(2- metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	6,9 (83)			
168	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-[(2- hidroxietil)amino]-3-(2- metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	0,32 (114)			>20 (0)
169	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-3-(2- metilpiridin-4-il)-5-[(oxan-4- il)amino]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (69)			>20 (54)
170	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-3-(2- metilpiridin-4-il)-5-[(1R,3r)-3- hidroxiciclobutil]amino}-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (37)			
171	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-3-(2- fluoropiridin-4-il)-5-(metilamino)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	24 (237)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
172	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-(dimetilamino)-3-(2-fluoropiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	16 (177)			
173	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-3-(2-fluoropiridin-4-il)-5-[(2-hidroxietil)amino]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	27 (54)			
174	(1R,2R,3S,4R,5R)-N-(5,6-dicloropiridin-3-il)-3-(2-fluoropiridin-4-il)-5-(metilamino)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (37)			
175	(1R,2R,3S,4R,5R)-N-(5,6-dicloropiridin-3-il)-5-(dimetilamino)-3-(2-fluoropiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	29 (186)			
176	(1R,2R,3S,4R,5R)-N-(5,6-dicloropiridin-3-il)-3-(2-fluoropiridin-4-il)-5-[(2-hidroxietil)amino]-7-oxabicyclo[2.2.1]heptano-2-carboxamida	25 (51)			
177	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-3-(2-metilpiridin-4-il)-5-(morfolin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	22 (211)	1,5 (34)	>50 (33)	1,5 (103)
178	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-hidroxi-5-metil-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (1)			
179	(1S,2S,3R,4S,5S)-N-(3,4-diclorofenil)-5-hidroxi-5-metil-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	>50 (22)			

Ej. Nro.		(A) EC ₅₀ μM (% eficacia)	(B) EC ₅₀ μM (% eficacia)	(C) IC ₅₀ μM (% eficacia)	(D) IC ₅₀ μM (% eficacia)
180	(1R,2R,3S,4R,5R)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	30 (113)			11 (69)
181	(1S,2S,3R,4S,5S)-N-(3,4-diclorofenil)-5-hidroxi-3-(2-metilpiridin-4-il)-7-oxabicyclo[2.2.1]heptano-2-carboxamida	27 (243)			>20 (28)

Se comprenderá que todos los ejemplos y las realizaciones descriptas en la presente solo tienen fines ilustrativos, que a la luz de estos, diversos cambios y modificaciones se tornarán evidentes a las personas con experiencia en la técnica y que se han de incluir dentro del espíritu y la esfera de esta solicitud y del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes, y solicitudes de patente citadas en la presente se incorporan a modo de referencia a todo efecto.