

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
(Apoderado)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap.I ☒ Cap. II ☐
No. Sol. Internacional PCT/EP2008/058423
Fecha de Presentación Internacional 1/07/2009

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción: Folios: 98 a 204 30/12/2009
1.2. Reivindicaciones: Folios: 205 a 216 30/12/2009
 Folios: 235 a 245 21/05/2010
1.3. Prioridad: GB 0712887.9 03/07/2007
 GB 0804317.6 7/03/2008

2. Análisis de la prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

Título de la solicitud: DERIVADOS DE PIPERIDINA ÚTILES COMO ANTAGONISTAS DEL RECEPTOR OREXINA.

El problema planteado en esta solicitud consiste en la necesidad de compuestos antagonistas de orexina con una mayor biodisponibilidad oral y una solubilidad mayor

en medios fisiológicos.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos derivados de imidazo[1,2-a]piridin-2-ilmetilo antagonistas de orexina para el tratamiento de la obesidad y la diabetes tipo 2, trastornos del sueño, ansiedad, depresión y esquizofrenia.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D471/04; A61K31/437; A61P3/00.

4. De la solicitud de patente

4.1. Título

El título es bastante general y hace alusión al mecanismo de acción, por lo cual se sugiere al solicitante hacer la corrección necesaria.

4.2. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio, las reivindicaciones 21 y 22 carecen de preámbulo, por lo cual se sugiere que se redacten de tal manera que tengan las partes habituales: preámbulo y parte característica.

5. **Análisis de la(s) oposición(es):** (artículo 43 D. 486)

No se presentaron oposiciones al objeto reivindicado.

6. **Determinación del estado de la técnica:**

La fecha que se ha tenido en cuenta para determinar el estado de la técnica es:

Fecha de presentación de la solicitud prioritaria 3/07/2007

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontraron como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO03/002561	N-aroyl cyclic amine derivatives as orexin receptor antagonists	9/01/2003
D2	WO2006/094235	Fused heterocyclic compounds and their use as sirtuin modulators	8/09/2006

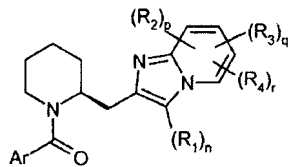
D1 (Fis. 252 a 255): divulga derivados N-aroyl-amina cíclica como antagonistas del receptor orexina.

D2 (Fis. 256 a 258): divulga compuestos heterocíclicos fusionados para el tratamiento de enfermedades tales como diabetes, obesidad y neurodegenerativas.

7. Examen de patentabilidad (artículo 14 D486)

7.1. Nivel inventivo (artículo 18 D486)

La presente solicitud de patente reivindica lo siguiente: un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo.



Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características técnicas esenciales	D1	D2
Ar= 	Ar ² = 	

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan compuestos derivados de imidazo[1,2-a]piridina sustituidos.

La diferencia entre la invención, definida en la reivindicación 1, y el compuesto del documento D1 consiste en que éste no contiene el grupo imidazo[1,2-a]piridin-2-il.

La diferencia entre la invención, definida en la reivindicación 1, y el compuesto del documento D2 consiste en las sustituciones en la posición 2 del grupo imidazo[1,2-a]piridin-2-il.

El efecto que confiere la diferencia es que se logran compuestos antagonistas de orexina para el tratamiento de la diabetes.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “¿cómo modificar el compuesto conocido en el documento D1 para lograr compuestos antagonistas de orexina para el tratamiento de la diabetes?”.

Sin embargo, la utilización de compuestos derivados de imidazo[1,2-a]piridinas para el tratamiento de la diabetes, ya está divulgada en el documento D2 que se refiere a compuestos derivados de imidazo[1,2-a]piridinas con actividad para tratar o prevenir

enfermedades como la diabetes, estrés, obesidad, entre otras.

La persona del oficio normalmente versada en la materia enfrentada con la tarea de proveer los compuestos derivados de piperidina con la actividad deseada puede darse cuenta que a partir de los documentos D1 y D2 los compuestos con un grupo imidazo[1,2-a]piridina con un patrón específico de sustitución, entre ellos lo que representa el grupo Ar de la presente solicitud, tendrá la actividad para el tratamiento de la diabetes.

En consecuencia, era obvio para la persona del oficio normalmente versada en la materia referirse a las enseñanzas divulgadas en el documento D2 con el fin de encontrar compuestos alternativos a los descritos en el documento D1 para llegar así al objeto de la reivindicación 1 de la solicitud.

En ausencia de un efecto inesperado mostrado por los compuestos reivindicados en relación con los compuestos del arte anterior, la solución al problema técnico parece ser obvia a la luz de los documentos D1 y D2.

Conclusión:
La reivindicación 1 no cumple con el requisito de nivel inventivo (Art. 18).

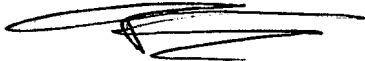
8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO03/002561	1 a 24	Nivel Inventivo
D2	WO2006/094235	1 a 24	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 17 ABO 2012

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0130342.9 19 December 2001 (19.12.2001) GB(71) Applicant (for all designated States except US):
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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

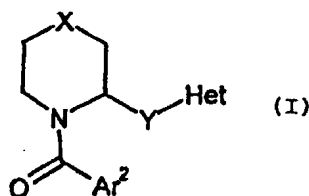
Published:

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guide
ance Notes on Codes and Abbreviations" appearing at the be-
ginning of each regular issue of the PCT Gazette.

WO 03/002561 A1

(54) Title: N-AROYL CYCLIC AMINE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS

(57) Abstract: This invention relates to N-aryl cyclic amine derivatives of formula (I),
wherein X represents a bond, oxygen, NR³ or a group (CH₂), wherein n represents 1, 2
or 3; Y represents CH₂, CO, CH(OH), or CH₂CH(OH); Het is an optionally substituted
bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; Ar²
represents an optionally substituted phenyl or a 5- or 6-membered heterocyclyl group con-
taining up to 3 heteroatoms selected from N, O and S and their use as pharmaceuticals,
specifically as orexin receptor antagonists.

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Example 39: (RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

A solution of 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (73mg, 0.33mmol), HATU (124mg, 0.33mmol) and *N,N*-diisopropylethylamine (0.35ml) in DMF (6ml) was stirred at room temperature under argon for 0.5h. The mixture was then treated with (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1H-benzoimidazole.2HCl, D20 (105mg, 0.33mmol) and stirring, under argon was continued for 16h. The reaction mixture was diluted with diethyl ether and washed with water (3X), dried (MgSO₄) and the solvent removed *in vacuo*. Chromatography (silica gel, ethyl acetate) afforded the title compound (88mg, 57%).

Mass spectrum (Electrospray LC/MS): Found 454 (MH⁺). C₂₄H₂₂F₃N₅O requires 453.

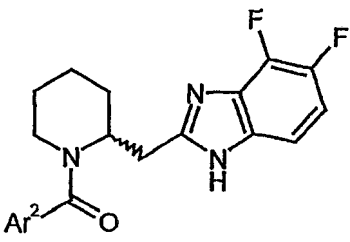
Example 40: (RS)-1-[2-(5-Methoxy-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

A stirring mixture of (1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid, D17 (150mg, 0.42mmol) and 4-methoxy-benzene-1,2-diamine (58mg, 0.42mmol) was heated at 120°C for 4h. The cooled reaction mixture was dissolved in ethyl acetate, washed with sodium hydrogen carbonate (2X) then brine. The solvent was removed *in vacuo* and the residue was chromatographed (silica gel, ethyl acetate) to afford the title compound as a brown gum (25mg, 13%).

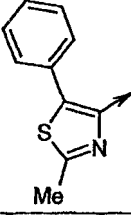
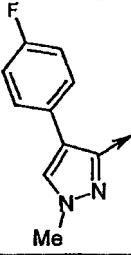
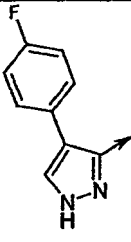
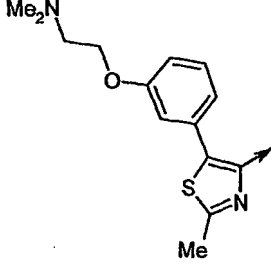
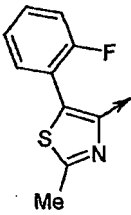
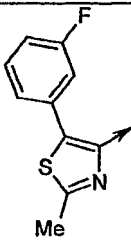
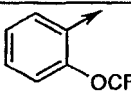
Mass spectrum (Electrospray LC/MS): Found 465 (MH⁺). C₂₅H₂₅FN₄O₂S requires 464.

The compounds of the Examples 41-50 and 92-108 were prepared from the appropriate carboxylic acid or acid chloride and (RS)-4,5-difluoro-2-piperidin-2-ylmethyl-1H-benzoimidazole, D21 using a similar procedure to that described in Example 2 or a procedure similar to that described in Examples 1 or 4. The compounds of Examples 47, 48 and 49 were converted to hydrochloride salts by treatment with 1M HCl in diethyl ether. The compound of Example 96 was prepared as the trifluoroacetate salt.

Table 3

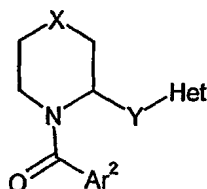


Example	Ar ²	Method	Mass Spectrum (Electrospray LC/MS)
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41		E2	Found MH ⁺ 453. C ₂₄ H ₂₂ F ₂ N ₄ OS requires 452.
42		E2	Found MH ⁺ 454. C ₂₄ H ₂₂ F ₃ N ₅ O requires 453.
43		E2	Found MH ⁺ 440. C ₂₃ H ₂₀ F ₃ N ₅ O requires 439.
44		E2	Found MH ⁺ 540. C ₂₈ H ₃₁ F ₂ N ₅ O ₂ S requires 539.
45		E4	Found MH ⁺ 471. C ₂₄ H ₂₁ F ₃ N ₄ OS requires 470.
46		E4	Found MH ⁺ 471. C ₂₄ H ₂₁ F ₃ N ₄ OS requires 470.
47		E2	Found MH ⁺ 440. C ₂₁ H ₁₈ F ₅ N ₃ O ₂ requires 439.

CLAIMS

1. A compound of formula (I):



wherein

- 10 X represents a bond, oxygen, NR³ or a group (CH₂)_n, wherein n represents 1, 2 or 3;
 Y represents CH₂, CO, CH(OH), or CH₂CH(OH);
 Het is an optionally substituted bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S;
 Ar² represents an optionally substituted phenyl or a 5- or 6-membered heterocyclyl group
 15 containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;
 R¹ represents hydrogen, optionally substituted (C₁₋₄)alkoxy, halo, cyano, optionally
 20 substituted (C₁₋₆)alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;
 R³ represents hydrogen or an optionally substituted (C₁₋₄)alkyl other than when Het is indolyl where R³ represents hydrogen or (C₁₋₄)alkyl;
 or a pharmaceutically acceptable salt thereof.
 25 with the proviso that;
 when X is NH, Y is CH₂ and Het is indolyl, Ar² is not 3,5-bis(trifluoromethyl)phenyl;
 or the compound is not
 (2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine;
 (2R)-2-[(1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl]benzoyl]piperazine;
 30 1-benzoyl-2-[(1H-indol-3-yl)methyl]piperazine.
2. A compound according to claim 1 wherein X is CH₂.
3. A compound according to claim 1 or 2 wherein Ar² represents optionally substituted
 35 phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazinyl, thienyl, naphthyl, triazolyl isoxazolyl, quinolinyl, or isoquinolinyl.
4. A compound according to any one of claims 1 to 3 wherein R¹ represents optionally substituted phenyl, pyridinyl, pyrazolyl pyrimidinyl or oxadiazolyl group.

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C07D 409/12 (2006.01) C07D 471/04 (2006.01)
C07D 409/04 (2006.01)

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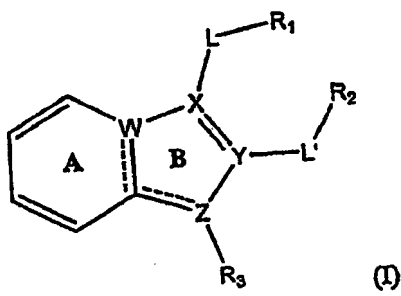
(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
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LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,
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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS SIRTUIN MODULATORS

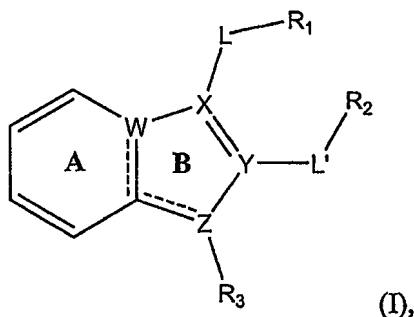


(57) Abstract: Provided herein are novel sirtuin-modulating compounds of formula (I) and methods of use thereof. The sirtuin-modulating compounds may be used for increasing the lifespan of a cell, and treating and preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, chemo therapeutic induced neuropathy, neuropathy associated with an ischemic event, polyglutamine diseases, ocular diseases and/or -disorders, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing. Also provided are compositions comprising a sirtuin-modulating compound in combination with another therapeutic agent.

WO 2006/094235 A1

What is claimed is:

1. A compound represented by Structural Formula (I):



or a salt thereof, wherein, as valence permits:

Ring A is optionally substituted;

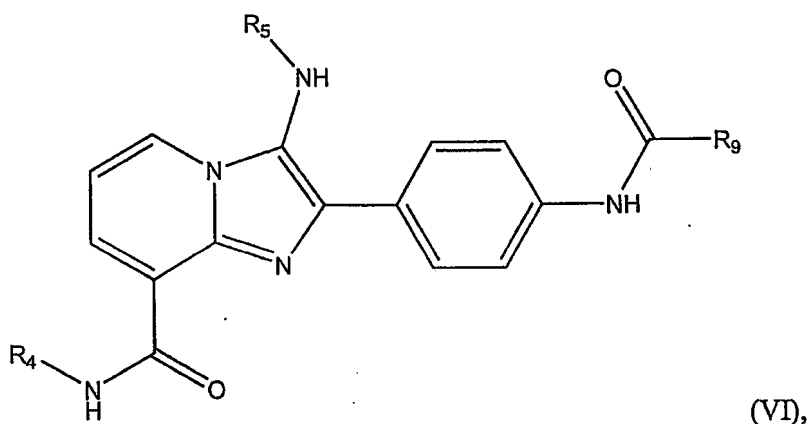
L is absent, substituted or unsubstituted phenylene, substituted or unsubstituted -O-phenylene, substituted or unsubstituted thienylene, substituted or unsubstituted pyrazolylene, substituted or unsubstituted benzothiazolylene, -NR₄-, -C(O)O-, -C(O)NR₄-, -NR₄C(O)-, -NR₄-C(O)-NR₅-, -S-, -CHR₆=CHR₇- or -CHR₆-C(O)-;

L' is absent, substituted or unsubstituted phenylene, substituted or unsubstituted -O-phenylene, substituted or unsubstituted thienylene, substituted or unsubstituted pyrazolylene, substituted or unsubstituted benzothiazolylene, substituted or unsubstituted indenedionylene, -C(O)O-, -C(O)NR₄-, -NR₄C(O)-, -NR₄-C(O)-NR₅-, -S-, -CHR₆=CHR₇- or -CHR₈-C(O)-, provided that at least one of L and L' is substituted or unsubstituted phenylene, substituted or unsubstituted -O-phenylene, substituted or unsubstituted thienylene, substituted or unsubstituted pyrazolylene, substituted or unsubstituted benzothiazolylene, substituted or unsubstituted indenedionylene, -NR₄-, -C(O)O-, -C(O)NR₄-, -NR₄C(O)-, -NR₄-C(O)-NR₅-, -S-, -CHR₆=CHR₇- or -CHR₈-C(O)-;

R₁ is absent, -H, -NR₄R₅, -N₄C(O)R₅, -OR₅, naphthyl or a heterocyclic group, provided that L and R₁ are not both absent unless X is N;

R₂ is -H, unsubstituted alkyl, -NR₄R₅, -NR₄C(O)R₅, -OR₅, substituted or unsubstituted phenyl, naphthyl or a heterocyclic group;

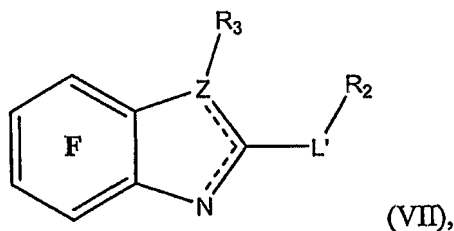
21. A compound represented by Structural Formula (VI):



or a salt thereof, wherein:

R₄, R₅ and R₉ are independently -H, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted non-aromatic heterocyclic group.

22. A compound represented by Structural Formula (VII):



or a salt thereof, wherein:

Ring F is optionally substituted;

L' is substituted or unsubstituted phenylene, substituted or unsubstituted thienylene, -C(O)O-, -NR₄C(O)-, -S-, -CHR₆=CHR₇- or -CHR₈-C(O)-;

R₂ is -H, unsubstituted alkyl, -NR₄R₅, -NR₄C(O)R₅, -OR₅, substituted or unsubstituted phenyl or a heterocyclic group;

R₃ is -H, -NR₄R₅, -N₄C(O)R₅, -OR₅ or a heterocyclic group, or R₂ and R₃, taken together with the atoms to which they are attached, form an optionally substituted heterocyclic group, or R₃ is absent when Z is O or S;