

São Paulo, March 21st 2022.

TO IPEA/BR

Applicant: ACHÉ LABORATÓRIOS FARMACÊUTICOS S.A
PCT/BR2021/050158 – International filing date: 15 April 2021
WO 2021/207816

Our ref.: ACHE-0136PCT / 1211-652_ PDI42

Dear Sirs,

Below you will find some arguments and amendments to the claims, according to article 34 and/or Rule 66.8 PCT, in response to form PCT/IPEA/404 (Rule 60.1 PCT), issued on February 02nd, 2022, to proceed with the international preliminary exam.

On the same date, we are presenting the payment of the preliminary exam fees (R\$630.00) and the Handling fee (200CHF = R\$1079.80), based on the conversion of March 18th, 2022).

➤ **Amendments:**

Claim 1 was withdrawn from the set of claims and the other claims were harmonized.

➤ **Arguments**

Two (2) documents were considered relevant by the International Searching Authority:

(D1) WO2018076090 from ACHE; and

(D2) Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews I Endocrinology, volume 15, February 2019, 105.

The present invention concerns a **specific** benzimidazole compound of **formula I** for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

In other words, the present invention refers to the use of the **specific** compound of **formula I** in the manufacture and use of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

The present invention also refers to a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising the specific compound of formula I and pharmaceutical acceptable excipients.

D1 belongs to the Applicant and **D2** is mentioned in the specification of the present application. Therefore, they are documents known to the Applicant.

As already described in the specification: Although the prior art suggests that drugs that regulate MT1/MT2 receptors might have a positive impact in the treatment of obesity, diabetes and liver metabolic diseases, drugs targeting specific melatonin receptors (MT1 or MT2) in peripheral tissues have never been developed.

This specific compound of the present invention i) acts as a melatonergic agonist with higher potency at MT1 than at MT2 receptor (see Table 1 in the specification) and ii) exhibit higher peripheral than central exposure, *i.e.*, low brain-to-plasma ratio (see Table 2 in the specification), thus acting preferentially on peripheral tissues.

The benzimidazole derivative of formula I according to the present invention is a potent, peripherally-preferred melatonin receptor agonist, with moderate selectivity toward the MT1 receptor, that regulates weight gain and insulin resistance, liver triglyceride levels and histology-determined steatosis. Thus, the benzimidazole derivative of formula I according to the present invention adds significant value to the treatment of obesity, diabetes and NAFLD/NASH.

The examples of the present invention address the advantageous effects of the specific compound of the present invention. In the Example 1, for instance, the effects of the benzimidazole derivative of formula I, a more potent agonist at MT1 than MT2, were compared to N-[3-(5-Chloro-2-ethoxy-6-methoxy-benzoimidazol-1-yl)-propyl]-acetamide (structure depicted below – formula II), a melatonergic agonist with higher potency at MT2 than MT1 receptors (*i.e.*, opposite of the benzimidazole derivative of formula I according to the present invention), and to those of dapagliflozin, a SGLT2 inhibitor that normalizes blood glucose levels and reduces body weight in DIO models (Millar P et al. (2017)).

According to the results, the treatment with compound of formula I notably reduced body weight, also significantly reduced plasma glucose and HOMA-IR, which is contrasted with the comparative compound (compound II) that did not significantly alter those parameters. Therefore, the use of melatonin receptor agonists in general does not teach *per se* someone skilled in the art to develop an efficacious compound for treating peripheral metabolic disorders.

Additionally, treatments with compound of formula I significantly reduced the liver triglyceride content and glycogen content, when compared to HFD Vehicle.

D1 refers to benzimidazole derivative compounds used for the treatment of psychiatric disorders and/or sleep disorders. **D1** does not relate to the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Many benzimidazole derivative compounds are describe in **D1**. There is no glue in **D1** to select **specifically** the compound I of the present invention to be used to treat obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. As the same way, the pharmaceutical compositions of **D1** are not related to treat obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

D2 is a review article that discuss the effect of melatonin and its receptors on glucose homeostasis, obesity and T2DM. According to this article, the studies did not solve the question of whether melatonin is beneficial or detrimental, and that clarifying the precise role of melatonin and its receptors on glucose homeostasis is urgent, as melatonin is widely used for other indications. Although **D2** mention diabetes and obesity, from the person skilled in the art point of view, there is no information from **D2** to guide a specialist in the art to particularly select the specific compound I of the present invention to be used to treat obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

A person skilled in the art would never be guided by the teachings of **D1** or **D2** to specifically select the compound I as claimed in the present invention, in order to be used for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Moreover, the specific findings of compound I on the regulation of liver metabolism have been disclosed **only in this particular patent application** but not in any prior art. Therefore, the present invention, as claimed is **NEW** and **INVENTIVE** in view of the teachings of **D1** or **D2**.

We believe that the amendments and arguments presented herewith are sufficient to clarify the questions raised in the international report and request that the amendments and arguments be considered for further examination.

We are at your entire disposal for any further clarifications.

Your Sincerely



Katia Jane Ferreira Evangelista



Paola Calabria Mattioli Dantas

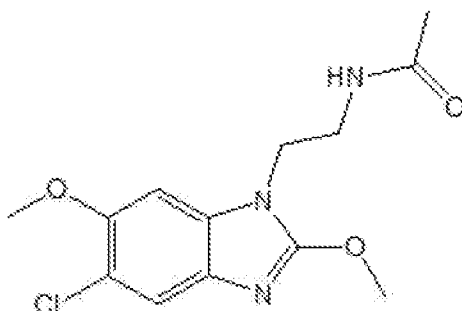
ANNEX - AMENDED SET OF CLAIMS.

ANNEX - AMENDED SET OF CLAIMS

Marked CLAIMS

~~{Claim 1}~~ A benzimidazole compound of formula I:

~~{Chem.1}~~

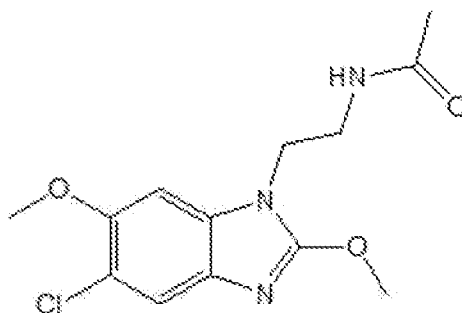


Formula I

~~or pharmaceutically acceptable salts, crystals, hydrates, solvates,
prodrugs or metabolites thereof.~~

~~{Claim 2}~~{Claim 1} -A benzimidazole compound of formula I for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis:

~~[Chem.2]~~[Chem.1]

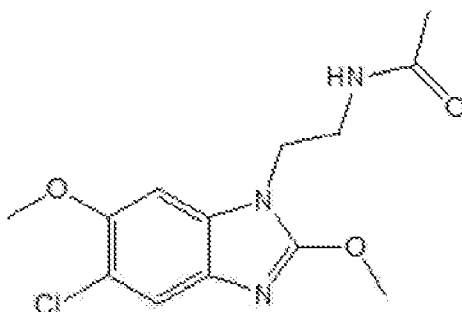


Formula I

or pharmaceutically acceptable salts, crystals, hydrates,
solvates, prodrugs or metabolites thereof.

~~{Claim 3}~~[Claim 2] Pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising a benzimidazole compound of formula I:

[Chem.32]



Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof and pharmaceutical acceptable excipients.

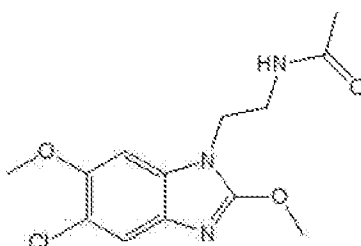
~~{Claim 4}~~[Claim 3] Pharmaceutical composition, according to claim 32, comprising 0.01 a 5000 mg of the benzimidazole compound of formula I.

~~{Claim 5}~~[Claim 4] ~~Pharmaceutically composition, according to claim 2, wherein~~
acceptable salts of benzimidazole compound of formula I ~~according to~~
~~claim 4~~are chosen from the inorganic addition salts hydrochloride, hydrobromide, sulfate, nitrate, phosphate; from the organic additions salts acetate, propionate, hexanoate, heptanoate, glycolate, piruvate, lactate, malonate, malate, maleate, fumarate, tartrate, citrate, succinate, mesylate, acistrate, besylate, tosylate, xinafoate, benzoate, p-toluenesulfonate, cinnamate, p-chlorobenzenesulfonate, 2-naphtalenesulfonate, p-toluenesulphonate, camphorsulfonate, trimethylacetate, t-butylacetate, laurylsulphate, gluconate, glutarate, hydroxynaphthoate, salicylate, stearate, muconate, mandelate, 2-hydroxyethanesulfonate; and from the alkaline addition salts of metals sodium, potassium, lithium, calcium, magnesium, bismuth, bromide; and from or pharmaceutically acceptable salts with the organic bases primary, secondary or tertiary amines; and salts with the aminoacid arginine,

lysine, histidine, caffeine, procaine, hydrobamine, choline, betaine, ethylenediamine, glycosamine, teobromine, purine, morpholine.

[Claim 6][Claim 5] Method for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising a benzimidazole compound of formula I:

[Chem. 45]



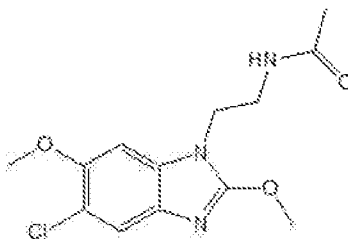
Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof.

[Claim 7][Claim 6] Method, according to claim 65, wherein 0.01 a 5000 mg of the benzimidazole compound of formula I is administered to a needed patient.

[Claim 8][Claim 7] Use of a benzimidazole compound in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis wherein the benzimidazole compound of formula I is:

[Chem. 55]



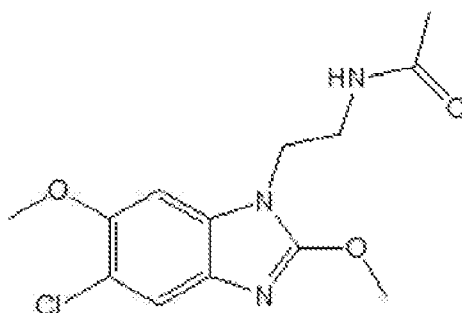
Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof.

CLAIMS

[Claim 1] A benzimidazole compound of formula I for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis:

[Chem.1]

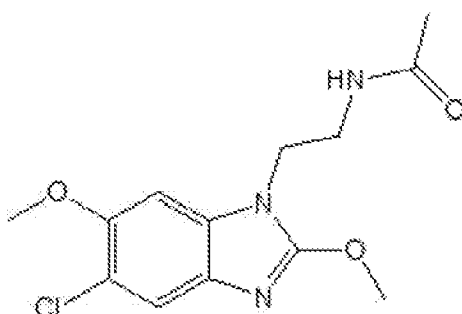


Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof.

[Claim 2] Pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising a benzimidazole compound of formula I:

[Chem.2]



Formula I

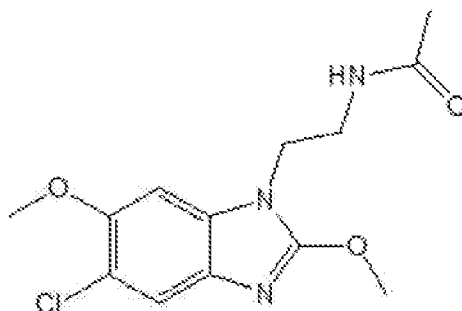
or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof and pharmaceutical acceptable excipients.

[Claim 3] Pharmaceutical composition, according to claim 2, comprising 0.01 a 5000 mg of the benzimidazole compound of formula I.

[Claim 4] Pharmaceutically composition, according to claim 2, wherein acceptable salts of benzimidazole compound of formula I are chosen from the inorganic addition salts hydrochloride, hydrobromide, sulfate, nitrate, phosphate; from the organic additions salts acetate, propionate, hexanoate, heptanoate, glycolate, piruvate, lactate, malonate, malate, maleate, fumarate, tartrate, citrate, succinate, mesylate, acistrate, besylate, tosylate, xinafoate, benzoate, p-toluenesulfonate, cinnamate, p-chlorobenzenesulfonate, 2-naphtalenesulfonate, p-toluenesulphonate, camphorsulfonate, trimethylacetate, t-butylacetate, laurylsulphate, gluconate, glutarate, hydroxynaphthoate, salicylate, stearate, muconate, mandelate, 2-hydroxyethanesulfonate; and from the alkaline addition salts of metals sodium, potassium, lithium, calcium, magnesium, bismuth, bromide; and from or pharmaceutically acceptable salts with the organic bases primary, secondary or tertiary amines; and salts with the aminoacid arginine, lysine, histidine, caffeine, procaine, hydrobamine, choline, betaine, ethylenediamine, glycosamine, teobromine, purine, morpholine.

[Claim 5] Method for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising a benzimidazole compound of formula I:

[Chem. 5]



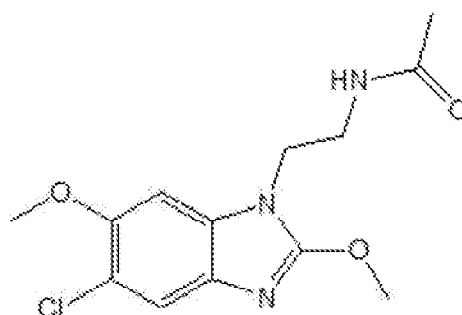
Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof.

[Claim 6] Method, according to claim 5, wherein 0.01 a 5000 mg of the benzimidazole compound of formula I is administered to a needed patient.

[Claim 7] Use of a benzimidazole compound in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis wherein the benzimidazole compound of formula I is:

[Chem.6]



Formula I

or pharmaceutically acceptable salts, crystals, hydrates, solvates, prodrugs or metabolites thereof.

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Bianca Elena Monteiro e Silva

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Message:

Dear Sirs,

Please, find attached our response to the Written Opinion of the International Preliminary Examining Authority, in response to the form PCT/IPEA/408 issued on May 10th, 2022, to be consider in the international preliminary exam.

Best regards,

The following documents have been uploaded via ePCT:

- Formal response to the IPEA (Rule 66.3)

Signature:	/KATIA JANE FERREIRA EVANGELISTA/
Signatory:	EVANGELISTA, Katia Jane Ferreira (Agent)
Date:	08 July 2022 14:08:59 BRT
User name:	Bianca Elena Monteiro e Silva
Authentication:	Sign-in with strong authentication

São Paulo, July 8th, 2022.

TO IPEA/BR

Applicant: ACHÉ LABORATÓRIOS FARMACÊUTICOS S.A

PCT/BR2021/050158 – International filing date: 15 April 2021

WO 2021/207816

Our ref.: ACHE-0136PCT / 1211-652_ PDI42

Dear Sirs,

Please, find below our response to the Written Opinion of the International Preliminary Examining Authority, in response to the form PCT/IPEA/408 issued on May 10th, 2022, to be consider in the international preliminary exam.

➤ **AS TO THE WRITTEN OPINION**

Following, we summarize the main points of the International Examination:

(Statement 1) No opinion was established for the claims 5 and 6, because said claims are related to the Method of Treatment of the human or animal body by therapy – Article 17(2)(a)(i) and Rule 67.1 (iv) (PCT).

(Statement 2) Cited documents: Reference was made to the same documents cited in Form PCT/ISA/237 - **(D1)** WO2018076090 from ACHE; and **(D2)** Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews I Endocrinology, volume 15, February 2019, 105. Claim 7 was considered new however lacks inventive activity and claims 1-4 were not considered new neither inventive.

(Statement 3) In the description there is no substantive information about the synthesis regarding the claimed compound (claim 1), and, therefore, compositions (claims 2 -4), thus there is no sufficiency disclosure for the matter claimed in claims 1-4, thus they are not in accordance with the Article 5 of the PCT.

➤ **OUR ARGUMENTS**

Regarding the **Statement 1**, the Applicant understands that the International Examining does not evaluate Method for the therapeutic treatment claims and clarifies that claims 5 and 6 will be maintained in the set of claims since the scope of those claims is allowed in some countries.

As to **Statement 2**, the Applicant noticed that the International Opinion over the two (2) prior art documents previously mentioned, was kept, and both documents were considered relevant by the International Examination Authority. The documents are listed below:

(D1) WO2018076090 from ACHE; and

(D2) Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews I Endocrinology, volume 15, February 2019, 105.

In view of this, the Applicant would like to point out that the present invention, as amended during the International Examination Request, does not refer to or claim a compound of **formula I** *per se*.

The present invention refers to the **specific** use of the **specific** compound of **formula I** for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; and to the **specific** use of the **specific** compound of **formula I** in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

The present invention also refers to a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis comprising the **specific** compound of formula I and pharmaceutical acceptable excipients.

The teachings of the prior art documents mentioned by the Examiner do not refer to this specific use and also do not guide a person skilled in the art to develop the present invention, *i.e* to use specifically the compound of formula for the matter claimed in the present application.

As stated before, **D1** belongs to the Applicant and **D2** is mentioned in the specification of the present application. Therefore, both documents are specially known to the Applicant, who does not have the necessity to claim an object that would already been (in theory) within the scope of a patent that belongs to the Applicant.

As already described in the specification of the present application **drugs targeting specific melatonin receptors (MT1 or MT2) in peripheral tissues have never been developed.**

However, the inventors of the present invention were able to surprisingly develop that the specific compound of formula I: i) acts as a melatonergic agonist with higher potency at MT1 than at MT2 receptor (see Table 1 in the specification) and ii) exhibit higher peripheral than central exposure, *i.e.*, low brain-to-plasma ratio (see Table 2 in the specification), thus acting preferentially on peripheral tissues.

Therefore, the **specific** benzimidazole derivative of formula I according to the present invention has surprisingly showed that is a potent, peripherally-preferred melatonin receptor agonist, with moderate selectivity toward the MT1 receptor, which regulates weight gain and insulin resistance, liver triglyceride levels and histology-determined steatosis. Thus, the benzimidazole derivative of formula I according to the present invention adds significant and unexpected value to the treatment of obesity, diabetes, and NAFLD/NASH.

The examples of the present invention address the advantageous effects of the **specific** compound of the present invention. In the Example 1, for instance, the effects of the benzimidazole derivative of formula I, a more potent agonist at MT1 than MT2, were compared to N-[3-(5-Chloro-2-ethoxy-6-methoxy-benzoimidazol-1-yl)-propyl]-acetamide (structure depicted below – formula II), a melatonergic agonist with higher potency at MT2 than MT1 receptors (*i.e.*, opposite of the benzimidazole derivative of formula I according to the present invention), and to those of dapagliflozin, a SGLT2 inhibitor that normalizes blood glucose levels and reduces body weight in DIO models (Millar P et al. (2017)).

According to the results, the treatment with **specific** compound of formula I notably reduced body weight, also significantly reduced plasma glucose and HOMA-IR, **which is contrasted with the comparative compound (compound II) that did not significantly alter those parameters.**

Therefore, as showed in the examples of the present application, the use of melatonin receptor agonists **in general** would not guide someone skilled in the art to develop the specific compound of formula I, which was particularly efficacious in the investigated in vivo models, for treating peripheral metabolic disorders.

D1 refers to benzimidazole derivative compounds in general used for the treatment of psychiatric disorders and/or sleep disorders. **D1 DOES NOT** relate to the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. **Many** benzimidazole derivative compounds are describe in **D1** and there is no clue in **D1** to select **specifically** the compound I of the present invention, within a wide list of other compounds described in **D1**, to be used specifically to treat obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

D2 is a review article that discuss the effect of melatonin and its receptors on glucose homeostasis, obesity and T2DM. According to this article, the studies did not solve the question of whether melatonin is beneficial or detrimental, and that clarifying

the precise role of melatonin and its receptors on glucose homeostasis is urgent, as melatonin is widely used for other indications and has a pleiotropic effect, including antioxidative activity that does not depend on its action at the MT1/2 receptors.

From the person skilled in the art point of view, there is no information from **D2** to guide a specialist in the art to select particularly the specific compound I of the present invention to be used to treat obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

Therefore, the Applicant states that a person skilled in the art would never be guided by the teachings of **D1** and/or **D2**, to select **specifically** the compound I as claimed in the present invention, in order to be used **specifically** for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, and achieve with high chances of success the advantages of those specific selections, as demonstrated by the examples of the present application.

Moreover, it is important to emphasize that the specific findings that the compound I acts on the regulation of liver metabolism, have been identified and disclosed **only in this particular patent application.** There is no information about this specific achievement in any prior art reference.

Therefore, for all stated above, the Applicant affirms that the present invention, as claimed, is **NEW** and **INVENTIVE** in view of the teachings of **D1** and/or **D2**.

As to **Statement 3**, the Applicant respectfully disagree with the International Opinion on lack of sufficiency disclosure for the claimed matter. Firstly, it is important to point out that the subject matter claimed, based on the current set of claims, finds support in the specification as filed. Regarding the synthesis of the compound of formula I, the Applicant reiterates that the present invention does not refer or claim to the compound of **formula I per se**. In addition, the process to obtain such compound is not part of the present invention as well.

Therefore, the description of the synthesis of the compound of formula I is not necessary since it is not related to the scope of the present invention. A person skilled in the art will be able to understand and reproduce the present invention based on the specification as filed and published.

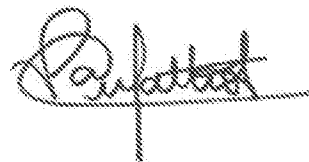
The Applicant trusts that the arguments presented herewith are sufficient to clarify the questions raised in the Written Opinion of the International Preliminary Examining Authority, and request that the arguments be considered for further examination.

We are at your entire disposal for any further clarifications.

Your Sincerely



Katia Jane Ferreira Evangelista



Paola Calabria Mattioli Dantas

Sao Paulo, 21 de marzo de 2022.

DIRIGIDO A IPEA/BR

Solicitante: ACHÉ LABORATÓRIOS FARMACÊUTICOS S.A.
PCT/BR2021/050158 – Fecha de presentación internacional: 15 de abril de 2021
WO 2021/207816

Nuestra ref.: ACHE-0136PCT / 1211-652_PDI42

Estimados señores,

A continuación, encontrarán algunos argumentos y modificaciones a las reivindicaciones, de conformidad con el artículo 34 y/o la Regla 66.8 PCT, en respuesta al formulario PCT/IPEA/404 (Regla 60.1 PCT), emitido el 02 de febrero de 2022, para proceder con el examen preliminar internacional.

En la misma fecha, estamos presentando el pago de la tasa del examen preliminar (R\$ 630,00) y la tasa de tramitación (200CHF = R\$ 1079,80), con base en la conversión del 18 de marzo de 2022).

➤ **Modificaciones:**

La reivindicación 1 fue retirada del capítulo reivindicatorio y se ajustaron las demás reivindicaciones.

➤ **Argumentos:**

La Administración encargada de la búsqueda internacional consideró pertinentes dos (2) documentos:

(D1) WO2018076090 de ACHE; y

(D2) Angeliki Karamitri y Ralf Jockers, *Melatonin in type 2 diabetes mellitus and obesity*, *Nature Reviews Endocrinology*, volumen 15, Febrero 2019, 105.

La presente invención se relaciona con un compuesto de bencimidazol **específico** de **fórmula I** para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

En otras palabras, la presente invención se relaciona con el uso del compuesto **específico** de **fórmula I** en la fabricación y el uso de una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

La presente invención también se relaciona con una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende el compuesto específico de fórmula I y excipientes farmacéuticamente aceptables.

D1 pertenece al Solicitante y **D2** se menciona en la memoria descriptiva de la presente solicitud. Por tanto, son documentos conocidos por el Solicitante.

Como ya se describió en la memoria descriptiva: aunque el estado de la técnica sugiere que los fármacos que regulan los receptores MT1/MT2 podrían tener un impacto positivo en el tratamiento de la obesidad, la diabetes y las enfermedades metabólicas hepáticas, nunca se han desarrollado fármacos dirigidos a receptores de melatonina específicos (MT1 o MT2) en tejidos periféricos.

Este compuesto específico de la presente invención i) actúa como un agonista melatonérgico con mayor potencia en el receptor MT1 que en el receptor MT2 (véase Tabla 1 en la memoria descriptiva) y ii) muestra una exposición periférica más alta que la central, es decir, una relación cerebro-plasma baja. (véase Tabla 2 en la memoria descriptiva), actuando así preferentemente sobre los tejidos periféricos.

El derivado de bencimidazol de fórmula I según la presente invención es un potente agonista del receptor de melatonina preferido periféricamente, con selectividad moderada hacia el receptor MT1, que regula el aumento de peso y la resistencia a la insulina, los niveles de triglicéridos hepáticos y la esteatosis determinada por histología. Por tanto, el derivado de bencimidazol de fórmula I según la presente invención añade un valor significativo al tratamiento de la obesidad, diabetes y NAFLD/NASH.

Los ejemplos de la presente invención abordan los efectos ventajosos del compuesto específico de la presente invención. En el Ejemplo 1, por ejemplo, los efectos del derivado de bencimidazol de fórmula I, un agonista más potente en MT1 que en MT2, se compararon con N-[3-(5-Cloro-2-etoxi-6-metoxi-benzoimidazol-1-il)-propil]-acetamida (estructura representada a continuación - fórmula II), un agonista melatonérgico con mayor potencia en los receptores MT2 que en los receptores MT1 (es decir, opuesto al derivado de bencimidazol de fórmula I según la presente invención), y a aquellos de dapagliflozina, un inhibidor de SGLT2 que normaliza los niveles de glucosa en sangre y reduce el peso corporal en modelos DIO (Millar Pet al. (2017).

De acuerdo a los resultados, el tratamiento con el compuesto de fórmula I redujo notablemente el peso corporal, también redujo significativamente la glucosa plasmática y el HOMA-IR, lo cual se contrasta con el compuesto comparativo (compuesto II) que no alteró significativamente dichos parámetros. Por lo tanto, el uso de agonistas del receptor de melatonina en general no enseña *per se* a un experto en la materia a desarrollar un compuesto eficaz para tratar trastornos metabólicos periféricos.

Además, los tratamientos con el compuesto de fórmula I redujeron significativamente el contenido de triglicéridos hepáticos y el contenido de glucógeno, en comparación con el vehículo HFD.

D1 se relaciona con compuestos derivados de bencimidazol utilizados para el tratamiento de trastornos psiquiátricos y/o trastornos del sueño. **D1** no se relaciona con el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica. Muchos compuestos derivados de bencimidazol se describen en **D1**. No hay ningún indicio en **D1** para seleccionar específicamente el compuesto I de la presente invención para usar en el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica. Del mismo modo, las composiciones farmacéuticas de **D1** no están relacionadas con el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

D2 es un artículo de revisión que analiza el efecto de la melatonina y sus receptores en la homeostasis de la glucosa, la obesidad y la T2DM. Según este artículo, los estudios no resolvieron la cuestión de si la melatonina es beneficiosa o perjudicial, y es urgente aclarar el papel preciso de la melatonina y sus receptores en la homeostasis de la glucosa, ya que la melatonina se usa ampliamente para otras indicaciones. Aunque **D2** menciona la diabetes y la obesidad, desde el punto de vista del experto en la materia, no existe información de **D2** que guíe a un especialista en la materia a seleccionar particularmente el compuesto I específico de la presente invención a utilizar para tratar la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

Una persona versada en la materia nunca se guiará por las enseñanzas de **D1** o **D2** para seleccionar específicamente el compuesto I como se reivindica en la presente invención, con el fin de ser utilizado para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica. Además, los descubrimientos específicos del compuesto I sobre la regulación del metabolismo hepático se han divulgado sólo en esta solicitud de patente en particular, pero no en ningún arte previo. Por lo tanto, la presente invención, tal como se reivindica, es **NUEVA** e **INVENTIVA** en vista de las enseñanzas de **D1** o **D2**.

Aoki, Ferreira,
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Creemos que las modificaciones y los argumentos presentados aquí son suficientes para aclarar las preguntas planteadas en el informe internacional y solicitamos que las modificaciones y los argumentos sean considerados para un examen más detenido.

Quedamos a su entera disposición para cualquier aclaración adicional.

Atentamente,

[Firmado]
Katia Jane Ferreira Evangelista

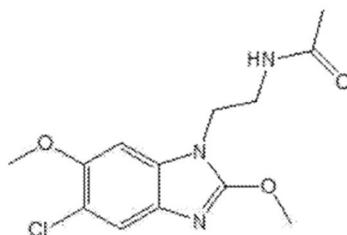
[Firmado]
Paola Calabria Mattioli Dantas

ANEXO – CAPÍTULO REIVINDICATORIO MODIFICADO.

ANEXO – CAPÍTULO REIVINDICATORIO MODIFICADO.

REIVINDICACIONES marcadas

~~[Reivindicación 1] — Un compuesto de bencimidazol de fórmula I:~~
~~[Quím.1]~~

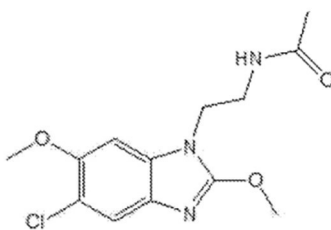


Fórmula I

~~o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.~~

~~[Reivindicación 2]~~ [Reivindicación 1] Un compuesto de bencimidazol de fórmula I para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica:

~~[Quím.21]~~

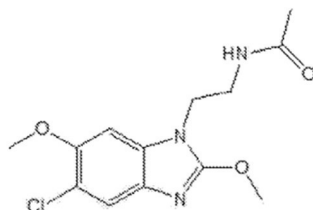


Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

[Reivindicación 3] [Reivindicación 2] Composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende un compuesto de bencimidazol de fórmula I:

[Quím.32]



Fórmula I

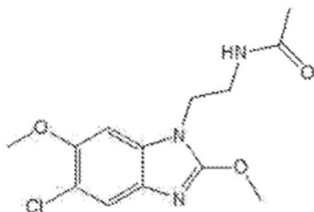
o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos y excipientes farmacéuticamente aceptables.

[Reivindicación 4] [Reivindicación 3] Composición farmacéutica, según la reivindicación 32, que comprende de 0,01 a 5000 mg del compuesto bencimidazol de fórmula I.

[Reivindicación 5] [Reivindicación 4] Composición farmacéutica, según la reivindicación 2, en donde las sales aceptables del compuesto de bencimidazol de fórmula I según la reivindicación 1 se eligen entre las sales de adición inorgánicas clorhidrato, bromhidrato, sulfato, nitrato, fosfato; de las sales de adición orgánicas acetato, propionato, hexanoato, heptanoato, glicolato, piruvato, lactato, malonato, malato, maleato, fumarato, tartrato, citrato, succinato, mesilato, acitrato, besilato, tosilato, xinafoato, benzoato, p-toluenosulfonato, cinamato, p-clorobencenosulfonato, 2-naftalenosulfonato, p-toluenosulfonato, canforsulfonato, trimetilacetato, t-butilacetato, laurilsulfato, gluconato, glutarato, hidroxinaftoato, salicilato, estearato, muconato, mandelato, 2-hidroxietanosulfonato; y de las sales de adición alcalina de los metales sodio, potasio, litio, calcio, magnesio, bismuto, bromuro; y de sales farmacéuticamente aceptables con las bases orgánicas aminas primarias, secundarias o terciarias; y sales con el aminoácido arginina, lisina, histidina, cafeína, procaína, hidrobamina, colina, betaína, etilendiamina, glucosamina, teobromina, purina, morfolina.

~~[Reivindicación 6]~~ [Reivindicación 5] Método para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende un compuesto de bencimidazol de fórmula I:

[Quím. 45]



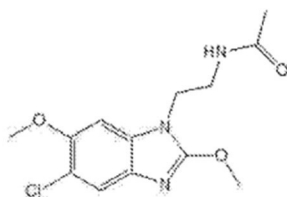
Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

~~[Reivindicación 7]~~ [Reivindicación 6] Método, según la reivindicación 5, en donde se administran de 0,01 a 5000 mg del compuesto de bencimidazol de fórmula I a un paciente que lo necesita.

~~[Reivindicación 8]~~ [Reivindicación 7] Uso de un compuesto de bencimidazol en la fabricación de una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica en donde el compuesto de bencimidazol de fórmula I es:

[Quím. 56]



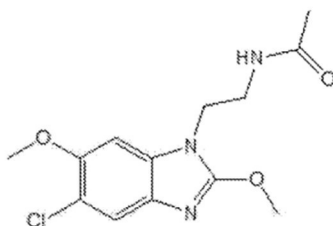
Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

REIVINDICACIONES

[Reivindicación 1] Un compuesto de bencimidazol de fórmula I para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica:

[Quím.1]

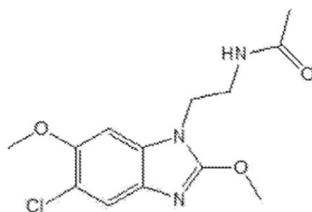


Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

[Reivindicación 2] Composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende un compuesto de bencimidazol de fórmula I:

[Quím.2]



Fórmula I

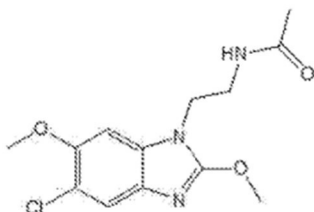
o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos y excipientes farmacéuticamente aceptables.

[Reivindicación 3] Composición farmacéutica, según la reivindicación 2, que comprende de 0,01 a 5000 mg del compuesto bencimidazol de fórmula I.

[Reivindicación 4] Composición farmacéutica, según la reivindicación 2, en donde las sales aceptables del compuesto de bencimidazol de fórmula I se eligen entre las sales de adición inorgánicas clorhidrato, bromhidrato, sulfato, nitrato, fosfato; de las sales de adición orgánicas acetato, propionato, hexanoato, heptanoato, glicolato, piruvato, lactato, malonato, malato, maleato, fumarato, tartrato, citrato, succinato, mesilato, acitrato, besilato, tosilato, xinafoato, benzoato, p-toluenosulfonato, cinamato, p-clorobencenosulfonato, 2-naftalenosulfonato, p-toluenosulfonato, canforsulfonato, trimetilacetato, t-butilacetato, laurilsulfato, gluconato, glutarato, hidroxinaftoato, salicilato, estearato, muconato, mandelato, 2-hidroxietanosulfonato; y de las sales de adición alcalina de los metales sodio, potasio, litio, calcio, magnesio, bismuto, bromuro; y de sales farmacéuticamente aceptables con las bases orgánicas aminas primarias, secundarias o terciarias; y sales con el aminoácido arginina, lisina, histidina, cafeína, procaína, hidrobamina, colina, betaína, etilendiamina, glucosamina, teobromina, purina, morfolina.

[Reivindicación 5] Método para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende un compuesto de bencimidazol de fórmula I:

[Quím. 5]



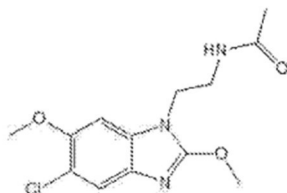
Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

[Reivindicación 6] Método, según la reivindicación 5, en donde se administran de 0,01 a 5000 mg del compuesto de bencimidazol de fórmula I a un paciente que lo necesita.

[Reivindicación 7] Uso de un compuesto de bencimidazol en la fabricación de una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica en donde el compuesto de bencimidazol de fórmula I es:

[Quím.6]



Fórmula I

o sales, cristales, hidratos, solvatos, profármacos farmacéuticamente aceptables o sus metabolitos.

Carga de documentos ePCT

Número de AI:
PCT/BR2021/050158

Dirigido a:
IPEA/BR

Fecha en la Oficina del destinatario:
8 de julio de 2022 14:08:59 BRT

De:
Bianca Elena Monteiro e Silva

Derechos de acceso:
eOwner

Mensaje:

Estimados señores,

Le adjuntamos nuestra respuesta a la Opinión Escrita de la Administración encargada del Examen Preliminar Internacional, en respuesta al formulario PCT/IPEA/408 emitido el 10 de mayo de 2022, para ser considerado en el examen preliminar internacional.

Saludos,

Los siguientes documentos se han cargado a través de ePCT:

- Contestación formal a la I PEA (Regla 66.3)

Firma:	/KATIA JANE FERREIRA EVANGELISTA/
Firmante:	EVANGELISTA, Katia Jane Ferreira (Agente)
Fecha:	08 de julio de 2022 14:08:59 BRT
Nombre de usuario:	Bianca Elena Monteiro e Silva
Autenticación:	inicie de sesión con autenticación fuerte

Sao Paulo, 08 de julio de 2022.

DIRIGIDO A IPEA/BR

Solicitante: ACHÉ LABORATÓRIOS FARMACÊUTICOS S.A.
PCT/BR2021/050158 – Fecha de presentación internacional: 15 de abril de 2021
WO 2021/207816

Nuestra ref.: ACHE-0136PCT / 1211-652_PDI42

Estimados señores,

A continuación, encontrarán nuestra respuesta a la Opinión Escrita de la Administración encargada del examen preliminar internacional, en respuesta al formulario PCT/IPEA/408 emitido el 10 de mayo de 2022, para ser considerado en el examen preliminar internacional.

➤ **EN CUANTO A LA OPINIÓN ESCRITA**

A continuación, resumimos los puntos principales del Examen Internacional:

(Declaración 1) No se estableció opinión para las reivindicaciones 5 y 6, porque dichas reivindicaciones se relacionan con el Método de Tratamiento del cuerpo humano o animal mediante terapia - Artículo 17(2)(a)(i) y Regla 67.1 (iv)) (PCT).

(Declaración 2) Documentos citados: Se hizo referencia a los mismos documentos citados en el Formulario PCT/ISA/237 - **(D1)** WO2018076090 de ACHE; y **(D2)** Angeliki Karamitri y Ralf Jockers, *Melatonin in type 2 diabetes mellitus and obesity*, *Nature Reviews I Endocrinology*, volumen 15, Febrero 2019, 105. La reivindicación 7 se consideró nueva, sin embargo, carece de nivel inventivo y las reivindicaciones 1- 4 no se consideraron nuevas ni inventivas.

(Declaración 3) En la descripción no hay información de fondo sobre la síntesis del compuesto reivindicado (reivindicación 1) y, por lo tanto, de las composiciones (reivindicaciones 2-4), por lo que no existe una descripción suficiente de la materia reivindicada en las reivindicaciones 1-4, por lo que no están de acuerdo con el Artículo 5 del PCT.

➤ **NUESTROS ARGUMENTOS**

En cuanto a la **Declaración 1**, el Solicitante entiende que el Examen Internacional no evalúa el Método para las reivindicaciones de tratamiento terapéutico y aclara que las reivindicaciones 5 y 6 se mantendrán en el capítulo reivindicatorio, ya que el alcance de esas reivindicaciones está permitido en algunos países.

En cuanto a la **Declaración 2**, el Solicitante notó que se mantuvo la Opinión Internacional sobre los dos (2) documentos del estado de la técnica antes mencionados, y ambos documentos fueron considerados relevantes por la Administración encargada el Examen Internacional. Los documentos se enumeran a continuación:

(D1) WO2018076090 de ACHE; y

(D2) Angeliki Karamitri y Ralf Jockers, *Melatonin in type 2 diabetes mellitus and obesity*, *Nature Reviews Endocrinology*, volumen 15, Febrero 2019, 105.

En vista de esto, el Solicitante quisiera señalar que la presente invención, modificada durante la Solicitud del Examen Internacional, no se refiere ni reivindica un compuesto de **fórmula I per se**.

La presente invención se relaciona con el uso **específico** del compuesto **específico** de **fórmula I** para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica; y al uso **específico** del compuesto **específico** de **fórmula I** en la fabricación de una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

La presente invención también se relaciona con una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica que comprende el compuesto **específico** de fórmula I y excipientes farmacéuticamente aceptables.

Las enseñanzas de los documentos del estado de la técnica mencionados por el Examinador no se refieren a este uso específico y tampoco orientan a un experto en la materia a desarrollar la presente invención, es decir, a utilizar específicamente el compuesto de fórmula para la materia reivindicada en la presente solicitud.

Como se indicó anteriormente, **D1** pertenece al Solicitante y **D2** se menciona en la memoria descriptiva de la presente solicitud. Por lo tanto, ambos documentos son especialmente conocidos por el Solicitante, quien no tiene la necesidad de reivindicar un objeto que ya estaría (en teoría) dentro del alcance de una patente que pertenece al Solicitante.

Como ya se ha descrito en la memoria descriptiva de la presente solicitud, **nunca se han desarrollado fármacos dirigidos a receptores de melatonina específicos (MT1 o MT2) en tejidos periféricos.**

Sin embargo, los inventores de la presente invención pudieron desarrollar sorprendentemente que el compuesto específico de fórmula I: i) actúa como un agonista melatonérgico con mayor potencia en el receptor MT1 que en el receptor MT2 (véase Tabla 1 en la memoria descriptiva) y ii) muestra una exposición periférica más alta que la central, es decir, una relación cerebro-plasma baja. (véase Tabla 2 en la memoria descriptiva), actuando así preferentemente sobre los tejidos periféricos.

Por lo tanto, el derivado de bencimidazol **específico** de fórmula I según la presente invención ha demostrado sorprendentemente que es un potente agonista del receptor de melatonina preferido periféricamente, con selectividad moderada hacia el receptor MT1, que regula el aumento de peso y la resistencia a la insulina, los niveles de triglicéridos hepáticos y la esteatosis determinada por histología. Por tanto, el derivado de bencimidazol de fórmula I según la presente invención añade un valor significativo e inesperado al tratamiento de la obesidad, diabetes y NAFLD/NASH.

Los ejemplos de la presente invención abordan los efectos ventajosos del compuesto **específico** de la presente invención. En el Ejemplo 1, por ejemplo, los efectos del derivado de bencimidazol de fórmula I, un agonista más potente en MT1 que en MT2, se compararon con N-[3-(5-Cloro-2-etoxi-6-metoxi-benzoimidazol-1-il)-propil]-acetamida (estructura representada a continuación - fórmula II), un agonista melatonérgico con mayor potencia en los receptores MT2 que en los receptores MT1 (es decir, opuesto al derivado de bencimidazol de fórmula I según la presente invención), y a aquellos de dapagliflozina, un inhibidor de SGLT2 que normaliza los niveles de glucosa en sangre y reduce el peso corporal en modelos DIO (Millar Pet al. (2017).

Según los resultados, el tratamiento con el compuesto **específico** de fórmula I redujo notablemente el peso corporal, también redujo significativamente la glucosa plasmática y el HOMA-IR, **lo que se contrasta con el compuesto comparativo (compuesto II) que no alteró significativamente dichos parámetros.**

Por lo tanto, como se muestra en los ejemplos de la presente solicitud, el uso de agonistas de los receptores de melatonina **en general** no guiaría a un experto en la materia a desarrollar el compuesto específico de fórmula I, que fue particularmente eficaz en los modelos *in vivo* investigados, para tratar trastornos metabólicos periféricos.

D1 se refiere a compuestos derivados de bencimidazol usados en general para el tratamiento de trastornos psiquiátricos y/o trastornos del sueño. **D1 NO** se relaciona con el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica. **Muchos** compuestos derivados de bencimidazol se describen en **D1** y no hay ningún indicio en **D1** para seleccionar **específicamente** el compuesto I de la presente invención, dentro de una amplia lista de otros compuestos descritos en **D1**, para ser usados específicamente para tratar la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

D2 es un artículo de revisión que analiza el efecto de la melatonina y sus receptores en la homeostasis de la glucosa, la obesidad y la T2DM. Según este artículo, los estudios no resolvieron la cuestión de si la melatonina es beneficiosa o perjudicial, y es urgente aclarar el papel preciso de la melatonina y sus receptores en la homeostasis de la glucosa, ya que la melatonina se usa ampliamente para otras indicaciones y tiene un efecto pleiotrópico, que incluye actividad antioxidante que no depende de su acción en los receptores MT1/2.

Desde el punto de vista del experto en la materia, no existe información de **D2** que oriente a un especialista en la materia a seleccionar particularmente el compuesto I específico de la presente invención para ser utilizado en el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

Por lo tanto, el Solicitante manifiesta que un experto en la materia nunca se guiaría por las enseñanzas de **D1** y/o **D2**, para seleccionar **específicamente** el compuesto I como se reivindica en la presente invención, con el fin de ser utilizado **específicamente** para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica, y lograr con altas posibilidades de éxito las ventajas de esas selecciones específicas, como lo demuestran los ejemplos de la presente solicitud.

Además, es importante enfatizar que los hallazgos específicos de que el compuesto I actúa sobre la regulación del metabolismo hepático, han sido identificados y divulgados **únicamente en esta solicitud de patente en particular**. No hay información sobre este logro específico en ninguna referencia del arte previo.

Por lo tanto, por todo lo expuesto anteriormente, el Solicitante afirma que la presente invención, tal como se reivindica, es **NUEVA** e **INVENTIVA** en vista de las enseñanzas de **D1** y/o **D2**.

En cuanto a la **Declaración 3**, el Solicitante discrepa respetuosamente con la Opinión Internacional sobre la falta de divulgación suficiente para la materia reivindicada. En primer lugar, es importante señalar que la materia reivindicada, con base en el capítulo reivindicatorio, encuentra respaldo en la memoria descriptiva presentada. En cuanto a la síntesis del compuesto de fórmula I, el Solicitante reitera que la presente invención no se refiere ni reivindica el compuesto de fórmula I *per se*. Además, el proceso para obtener dicho compuesto tampoco forma parte de la presente invención.

Aoki, Ferreira,
Mattioli & Yamashita
Propiedade Intelectual

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LinkedIn: afmy

Por lo tanto, la descripción de la síntesis del compuesto de fórmula I no es necesaria ya que no está relacionada con el alcance de la presente invención. Un experto en la materia será capaz de comprender y reproducir la presente invención basándose en la memoria descriptiva tal como se presentó y publicó.

El Solicitante confía en que los argumentos presentados en este documento son suficientes para aclarar las cuestiones planteadas en la Opinión Escrita de la Administración encargada del Examen Preliminar Internacional, y solicita que los argumentos sean considerados para un examen más detenido.

Quedamos a su entera disposición para cualquier aclaración adicional.

Atentamente,

[Firmado]
Katia Jane Ferreira Evangelista

[Firmado]
Paola Calabria Mattioli Dantas

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 ACHE-0136PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application N° PCT/BR2021/050158	International filing date (day/month/year) 15/04/2021	Priority Date (day/month/year) 15/04/2020
International Patent Classification (IPC) or national classification and IPC IPC: C07D235/26 (2006.01), A61K31/4184 (2006.01), A61P3/04 (2006.01), A61P3/10 (2006.01), A61P1/16 (2006.01) CPC: C07D235/26, A61K31/4184, A61P3/04, A61P3/10, A61P1/16		
Applicant ACHÉ LABORATÓRIOS FARMACÉUTICOS S.A		

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>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: d. ☒ (sent to the applicant and to the International Bureau) a total of <u>18</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)). e. ☐ (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 reports 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 14/02/2022	Date of completion of this report 01/08/2022
Name and mailing address of the ISA/BR INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Mayrink Veiga nº 9, 6º andar cep: 20090-910, Centro - Rio de Janeiro/RJ Facsimile N°: +55 21 3037-3663	Authorized officer Luiz Eduardo Kaercher Telephone N°: +55 21 3037-3686/3742

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 (Rules 12.3(a) and 23.1(b)).
- ☐ publication of the international application (Rule 12.4(a)).
- ☐ international preliminary examination (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*):

- ☐ the international application as originally filed/furnished.
- ☒ the description: pages **1 to 19** as originally filed/furnished.
 pages* _____ received by this Authority on _____
 pages* _____ received by this Authority on _____
- ☒ the claims: Nos. _____ as originally filed/furnished.
 Nos. * _____ as amended (together with any statement) under Article 19.
 Nos. * **1 to 7** received by this Authority on **14/02/2022**
- ☒ the drawings: pages **1 to 3** as originally filed/furnished.
 pages* _____ received by this Authority on _____
 pages* _____ received by this Authority on _____
- ☐ 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 **8**
- ☐ 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 amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)).

- ☐ the description, pages _____
- ☐ 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 (Rule 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)).

6. With regard to top-up searches (Rules 66.1ter and 70.2(f)):

- ☐ A top-up search was carried out by this Authority on _____
- ☐ 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)).

* *Se o item 4 for aplicado, algumas ou todas estas páginas podem ser marcadas "substituída".*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application N°

PCT/BR2021/050158

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5 and 6

because:

☒ the said international application, or the said claims Nos. 5 and 6
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Method of treatment of the human or animal body by therapy according to Article 17(2)(a)(i) and Rule 67.1 (iv) (PCT).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 5 and 6

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b) and 13 ter.2.

☐ See Supplemental Box for further details.

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

1. Statement

Novelty (N)	Claims	<u>7</u>	YES
	Claims	<u>1 to 4</u>	NO
Inventive step (IS)	Claims	<u>-----</u>	YES
	Claims	<u>1 to 4 and 7</u>	NO
Industrial applicability (IA)	Claims	<u>1 to 4 and 7</u>	YES
	Claims	<u>-----</u>	NO

2. Citations and explanations (Rule 70.7):

1) Cited documents: D1: WO 2018076090 A1 and D2: Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews | Endocrinology, volume 15, February 2019, 105. were considered relevant.

2) The claimed object is a specific benzimidazole compound of formula I for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

3) The applicant presented arguments in order to better define the invention and make clear the differences between the subject matter claimed in the present application and the cited state of the art.

According to the Applicant, (...) *the teachings of the prior art documents mentioned by the Examiner do not refer to this specific use and also do not guide a person skilled in the art to develop the present invention, i.e to use specifically the compound of formula for the matter claimed in the present application.*

(...) *drugs targeting specific melatonin receptors (MT1 or MT2) in peripheral tissues have never been developed. However, the inventors of the present invention were able to surprisingly develop that the specific compound of formula I: i) acts as a melatonergic agonist with higher potency at MT1 than at MT2 receptor (see Table 1 in the specification) and ii) exhibit higher peripheral than central exposure, i.e., low brain-to-plasma ratio (see Table 2 in the specification), thus acting preferentially on peripheral tissues.*

(...) *In the Example 1, for instance, the effects of the benzimidazole derivative of formula I, a more potent agonist at MT1 than MT2, were compared to N-[3-(5-Chloro-2-ethoxy-6-methoxy-benzimidazol-1-yl)-propyl]-acetamide (structure depicted below – formula II), a melatonergic agonist with higher potency at MT2 than MT1 receptors (i.e., opposite of the benzimidazole derivative of formula I according to the present invention), and to those of dapagliflozin, a SGLT2 inhibitor that normalizes blood glucose levels and reduces body weight in DIO models (Millar P et al. (2017).*

The compound claimed in claim 1, per se, is disclosed in D1 (compound 143, page 74, example 22) in addition to being specifically claimed in claim 3 of D1. Likewise, the compositions claimed in claims 2 to 4 are disclosed in D1 (claims 10 and 12), therefore claims 1 to 4 are not in accordance with Art. 33(2) and 33(3) PCT. The use (claim 7) of the compound of the Formula (I) in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is considered novel over the document D1, therefore claim 7 are in accordance with Art. 33(2) PCT.

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:

According to the applicant regarding the synthesis of the compound of formula I (...) *the present invention does not refer or claim to the compound of formula I per se. In addition, the process to obtain such compound is not part of the present invention as well.*

This International Searching Authority disagree as the compound and composition claims have been preserved in the set of claims.

Thus, there is no sufficiency disclosure for the matter claimed in claims 1-4, thus they are not in accordance with the Article 5 of the PCT.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box No. V**

However, as already considered, throughout the description of document D1 it is revealed that such compounds have affinity for melatonergic receptors and the document D2 reveals the direct association of these receptors with the pathologies linked to the claimed use. In this way, it is understood that from the information disclosed in the documents D1 and D2, a person skill in the art would achieve at the matter claimed. Thus, the claim 7 are not in accordance with Art. 33(3) PCT.

4) The industrial applicability for the claims 1 – 4 and 7 is beyond any doubt in accordance with the art. 33 (4) PCT.

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 ACHE-0136PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application N° PCT/BR2021/050158	International filing date (day/month/year) 15/04/2021	Priority Date (day/month/year) 15/04/2020
International Patent Classification (IPC) or national classification and IPC IPC: C07D235/26 (2006.01), A61K31/4184 (2006.01), A61P3/04 (2006.01), A61P3/10 (2006.01), A61P1/16 (2006.01) CPC: C07D235/26, A61K31/4184, A61P3/04, A61P3/10, A61P1/16		
Applicant ACHÉ LABORATÓRIOS FARMACÊUTICOS S.A		

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>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: d. ☒ (sent to the applicant and to the International Bureau) a total of <u>18</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)). e. ☐ (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 reports 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 14/02/2022	Date of completion of this report 01/08/2022
Name and mailing address of the ISA/BR INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Mayrink Veiga nº 9, 6º andar cep: 20090-910, Centro - Rio de Janeiro/RJ Facsimile N°: +55 21 3037-3663	Authorized officer Luiz Eduardo Kaercher Telephone N°: +55 21 3037-3686/3742

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 (Rules 12.3(a) and 23.1(b)).
- ☐ publication of the international application (Rule 12.4(a)).
- ☐ international preliminary examination (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*):

- ☐ the international application as originally filed/furnished.
- ☒ the description: pages **1 to 19** as originally filed/furnished.
 pages* _____ received by this Authority on _____
 pages* _____ received by this Authority on _____
- ☒ the claims: Nos. _____ as originally filed/furnished.
 Nos. * _____ as amended (together with any statement) under Article 19.
 Nos. * **1 to 7** received by this Authority on **14/02/2022**
- ☒ the drawings: pages **1 to 3** as originally filed/furnished.
 pages* _____ received by this Authority on _____
 pages* _____ received by this Authority on _____
- ☐ 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 **8**
- ☐ 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 amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)).

- ☐ the description, pages _____
- ☐ 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 (Rule 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)).

6. With regard to top-up searches (Rules 66.1ter and 70.2(f)):

- ☐ A top-up search was carried out by this Authority on _____
- ☐ 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)).

* *Se o item 4 for aplicado, algumas ou todas estas páginas podem ser marcadas "substituída".*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application N°

PCT/BR2021/050158

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. **5 and 6**

because:

☒ the said international application, or the said claims Nos. **5 and 6**
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Method of treatment of the human or animal body by therapy according to Article 17(2)(a)(i) and Rule 67.1 (iv) (PCT).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. **5 and 6**

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b) and 13 ter.2.

☐ See Supplemental Box for further details.

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

1. Statement

Novelty (N)	Claims	7	YES
	Claims	1 to 4	NO
Inventive step (IS)	Claims	-----	YES
	Claims	1 to 4 and 7	NO
Industrial applicability (IA)	Claims	1 to 4 and 7	YES
	Claims	-----	NO

2. Citations and explanations (Rule 70.7):

1) Cited documents: D1: WO 2018076090 A1 and D2: Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews | Endocrinology, volume 15, February 2019, 105. were considered relevant.

2) The claimed object is a specific benzimidazole compound of formula I for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

3) The applicant presented arguments in order to better define the invention and make clear the differences between the subject matter claimed in the present application and the cited state of the art.

According to the Applicant, (...) *the teachings of the prior art documents mentioned by the Examiner do not refer to this specific use and also do not guide a person skilled in the art to develop the present invention, i.e to use specifically the compound of formula for the matter claimed in the present application.*

(...) *drugs targeting specific melatonin receptors (MT1 or MT2) in peripheral tissues have never been developed. However, the inventors of the present invention were able to surprisingly develop that the specific compound of formula I: i) acts as a melatonergic agonist with higher potency at MT1 than at MT2 receptor (see Table 1 in the specification) and ii) exhibit higher peripheral than central exposure, i.e., low brain-to-plasma ratio (see Table 2 in the specification), thus acting preferentially on peripheral tissues.*

(...) *In the Example 1, for instance, the effects of the benzimidazole derivative of formula I, a more potent agonist at MT1 than MT2, were compared to N-[3-(5-Chloro-2-ethoxy-6-methoxy-benzimidazol-1-yl)-propyl]-acetamide (structure depicted below – formula II), a melatonergic agonist with higher potency at MT2 than MT1 receptors (i.e., opposite of the benzimidazole derivative of formula I according to the present invention), and to those of dapagliflozin, a SGLT2 inhibitor that normalizes blood glucose levels and reduces body weight in DIO models (Millar P et al. (2017).*

The compound claimed in claim 1, per se, is disclosed in D1 (compound 143, page 74, example 22) in addition to being specifically claimed in claim 3 of D1. Likewise, the compositions claimed in claims 2 to 4 are disclosed in D1 (claims 10 and 12), therefore claims 1 to 4 are not in accordance with Art. 33(2) and 33(3) PCT. The use (claim 7) of the compound of the Formula (I) in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is considered novel over the document D1, therefore claim 7 are in accordance with Art. 33(2) PCT.

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:

According to the applicant regarding the synthesis of the compound of formula I (...) *the present invention does not refer or claim to the compound of formula I per se. In addition, the process to obtain such compound is not part of the present invention as well.*

This International Searching Authority disagree as the compound and composition claims have been preserved in the set of claims.

Thus, there is no sufficiency disclosure for the matter claimed in claims 1-4, thus they are not in accordance with the Article 5 of the PCT.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box No. V**

However, as already considered, throughout the description of document D1 it is revealed that such compounds have affinity for melatonergic receptors and the document D2 reveals the direct association of these receptors with the pathologies linked to the claimed use. In this way, it is understood that from the information disclosed in the documents D1 and D2, a person skill in the art would achieve at the matter claimed. Thus, the claim 7 are not in accordance with Art. 33(3) PCT.

4) The industrial applicability for the claims 1 – 4 and 7 is beyond any doubt in accordance with the art. 33 (4) PCT.

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 ACHE-0136PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application N° PCT/BR2021/050158	International filing date (day/month/year) 15/04/2021	Priority Date (day/month/year) 15/04/2020
International Patent Classification (IPC) or national classification and IPC IPC: C07D235/26 (2006.01), A61K31/4184 (2006.01), A61P3/04 (2006.01), A61P3/10 (2006.01), A61P1/16 (2006.01) CPC: C07D235/26, A61K31/4184, A61P3/04, A61P3/10, A61P1/16		
Applicant ACHÉ LABORATÓRIOS FARMACÉUTICOS S.A		

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Date of submission of the demand 14/02/2022	Date of completion of this report 01/08/2022
Name and mailing address of the ISA/BR INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Mayrink Veiga nº 9, 6º andar cep: 20090-910, Centro - Rio de Janeiro/RJ Facsimile N°: +55 21 3037-3663	Authorized officer Luiz Eduardo Kaercher Telephone N°: +55 21 3037-3686/3742

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 (Rules 12.3(a) and 23.1(b)).
- ☐ publication of the international application (Rule 12.4(a)).
- ☐ international preliminary examination (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*):

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pages* _____ received by this Authority on _____
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pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____
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3. ☒ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☒ the claims, Nos **8**
- ☐ 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 amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)).

- ☐ the description, pages _____
- ☐ 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 (Rule 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)).

6. With regard to top-up searches (Rules 66.1ter and 70.2(f)):

- ☐ A top-up search was carried out by this Authority on _____
- ☐ 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)).

* *Se o item 4 for aplicado, algumas ou todas estas páginas podem ser marcadas "substituída".*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application N°

PCT/BR2021/050158

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5 and 6

because:

☒ the said international application, or the said claims Nos. 5 and 6
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Method of treatment of the human or animal body by therapy according to Article 17(2)(a)(i) and Rule 67.1 (iv) (PCT).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 5 and 6

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b) and 13 ter.2.

☐ See Supplemental Box for further details.

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

1. Statement

Novelty (N)	Claims	<u>7</u>	YES
	Claims	<u>1 to 4</u>	NO
Inventive step (IS)	Claims	<u>-----</u>	YES
	Claims	<u>1 to 4 and 7</u>	NO
Industrial applicability (IA)	Claims	<u>1 to 4 and 7</u>	YES
	Claims	<u>-----</u>	NO

2. Citations and explanations (Rule 70.7):

1) Cited documents: D1: WO 2018076090 A1 and D2: Angeliki Karamitri and Ralf Jockers, Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews | Endocrinology, volume 15, February 2019, 105. were considered relevant.

2) The claimed object is a specific benzimidazole compound of formula I for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

3) The applicant presented arguments in order to better define the invention and make clear the differences between the subject matter claimed in the present application and the cited state of the art.

According to the Applicant, (...) *the teachings of the prior art documents mentioned by the Examiner do not refer to this specific use and also do not guide a person skilled in the art to develop the present invention, i.e to use specifically the compound of formula for the matter claimed in the present application.*

(...) *drugs targeting specific melatonin receptors (MT1 or MT2) in peripheral tissues have never been developed. However, the inventors of the present invention were able to surprisingly develop that the specific compound of formula I: i) acts as a melatonergic agonist with higher potency at MT1 than at MT2 receptor (see Table 1 in the specification) and ii) exhibit higher peripheral than central exposure, i.e., low brain-to-plasma ratio (see Table 2 in the specification), thus acting preferentially on peripheral tissues.*

(...) *In the Example 1, for instance, the effects of the benzimidazole derivative of formula I, a more potent agonist at MT1 than MT2, were compared to N-[3-(5-Chloro-2-ethoxy-6-methoxy-benzimidazol-1-yl)-propyl]-acetamide (structure depicted below – formula II), a melatonergic agonist with higher potency at MT2 than MT1 receptors (i.e., opposite of the benzimidazole derivative of formula I according to the present invention), and to those of dapagliflozin, a SGLT2 inhibitor that normalizes blood glucose levels and reduces body weight in DIO models (Millar P et al. (2017).*

The compound claimed in claim 1, per se, is disclosed in D1 (compound 143, page 74, example 22) in addition to being specifically claimed in claim 3 of D1. Likewise, the compositions claimed in claims 2 to 4 are disclosed in D1 (claims 10 and 12), therefore claims 1 to 4 are not in accordance with Art. 33(2) and 33(3) PCT. The use (claim 7) of the compound of the Formula (I) in the manufacture of a pharmaceutical composition for the treatment of obesity, diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is considered novel over the document D1, therefore claim 7 are in accordance with Art. 33(2) PCT.

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:

According to the applicant regarding the synthesis of the compound of formula I (...) *the present invention does not refer or claim to the compound of formula I per se. In addition, the process to obtain such compound is not part of the present invention as well.*

This International Searching Authority disagree as the compound and composition claims have been preserved in the set of claims.

Thus, there is no sufficiency disclosure for the matter claimed in claims 1-4, thus they are not in accordance with the Article 5 of the PCT.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box No. V**

However, as already considered, throughout the description of document D1 it is revealed that such compounds have affinity for melatonergic receptors and the document D2 reveals the direct association of these receptors with the pathologies linked to the claimed use. In this way, it is understood that from the information disclosed in the documents D1 and D2, a person skill in the art would achieve at the matter claimed. Thus, the claim 7 are not in accordance with Art. 33(3) PCT.

4) The industrial applicability for the claims 1 – 4 and 7 is beyond any doubt in accordance with the art. 33 (4) PCT.

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en Materia de Patentes)

(PCT Artículo 36 y Regla 70)

Referencia de presentación del solicitante o agente ACHE-0136PCT	PARA ACCIÓN ADICIONAL véase Formulario PCT/IPEA/416																	
Solicitud internacional No. PCT/BR2021/050158	Fecha de presentación internacional (Día/Mes/Año) 15/04/2021	Fecha de prioridad (Día/Mes/Año) 15/04/2020																
Clasificación Internacional de Patentes (CIP) o clasificación nacional y CIP CIP: C07D235/26 (2006.01), A61K31/4184 (2006.01), A61P3/04 (2006.01), A61P3/10 (2006.01), A61P1/16 (2006.01) CPC: C07D235/26, A61K31/4184, A61P3/04, A61P3/10, A61P1/16																		
Solicitante ACHÉ LABORATORIOS FARMACÉUTICOS S.A																		
1. El presente informe es el informe del examen preliminar internacional, establecido por la Administración encargada del examen preliminar internacional de conformidad con el Artículo 35 y allegado al solicitante de conformidad con el Artículo 36. 2. El presente INFORME se compone de <u>6</u> hojas, incluida esta portada. 3. Este informe se encuentra igualmente acompañado de ANEXOS, los cuales comprenden: d. ☒ (enviado al solicitante y a la oficina internacional) un total de <u>18</u> hojas, como sigue: ☒ hojas de la descripción, las reivindicaciones y/o los dibujos modificados y/o las hojas que comprenden correcciones autorizadas por la Administración, a menos que dichas hojas hayan sido reemplazadas o canceladas, y cualquier carta adjunta (véase Reglas 46.5, 66.8, 70.16, 91.2 y Sección 607 de las Instrucciones Administrativas). ☐ hojas con correcciones, cuando esta Administración tomó la decisión de no tenerlas en cuenta porque no fueron autorizadas o notificadas en el momento en que esta Administración comenzó a redactar el presente informe, y cualquier carta adjunta (Reglas 66.4bis, 70.2 (e), 70.16 y 91.2). ☐ hojas de reemplazo y cartas adjuntas, cuando esta Administración considere que las hojas de reemplazo contienen una modificación que va más allá de la divulgación en la solicitud internacional presentada, o las hojas de reemplazo no fueron acompañadas por una carta que indique la base de las modificaciones en la solicitud presentada, como se indica en el ítem 4 del Recuadro No. I y el Recuadro Suplementario (véase Regla 70.16(b)). e. ☐ (enviado solamente a la Oficina Internacional) un total de (indique el tipo y número del vehículo(s) electrónico(s)), que contiene una lista de secuencias, en forma de archivo de texto del Anexo C/ST.25, como se indica en el Recuadro complementario relativo al listado de secuencias (véase el párrafo 3 del Anexo C de las Instrucciones Administrativas).																		
4. Este informe contiene indicaciones relacionadas con los siguientes elementos: <table border="0" style="width: 100%;"><tr><td>☒ Recuadro No. I</td><td>Base del informe</td></tr><tr><td>☐ Recuadro No. II</td><td>Prioridad</td></tr><tr><td>☒ Recuadro No. III</td><td>No se establece opinión con respecto a la novedad, el nivel inventivo y la aplicabilidad industrial</td></tr><tr><td>☐ Recuadro No. IV</td><td>Falta de unidad de invención</td></tr><tr><td>☒ Recuadro No. V</td><td>Declaración motivada de conformidad con el Artículo 35(2), en relación con la novedad, el nivel inventivo o la aplicabilidad industrial; citas y explicaciones que respaldan dicha declaración</td></tr><tr><td>☐ Recuadro No. VI</td><td>Ciertos documentos citados</td></tr><tr><td>☐ Recuadro No. VII</td><td>Ciertos defectos en la solicitud internacional</td></tr><tr><td>☒ Recuadro No. VIII</td><td>Ciertas observaciones sobre la solicitud internacional</td></tr></table>			☒ Recuadro No. I	Base del informe	☐ Recuadro No. II	Prioridad	☒ Recuadro No. III	No se establece opinión con respecto a la novedad, el nivel inventivo y la aplicabilidad industrial	☐ Recuadro No. IV	Falta de unidad de invención	☒ Recuadro No. V	Declaración motivada de conformidad con el Artículo 35(2), en relación con la novedad, el nivel inventivo o la aplicabilidad industrial; citas y explicaciones que respaldan dicha declaración	☐ Recuadro No. VI	Ciertos documentos citados	☐ Recuadro No. VII	Ciertos defectos en la solicitud internacional	☒ Recuadro No. VIII	Ciertas observaciones sobre la solicitud internacional
☒ Recuadro No. I	Base del informe																	
☐ Recuadro No. II	Prioridad																	
☒ Recuadro No. III	No se establece opinión con respecto a la novedad, el nivel inventivo y la aplicabilidad industrial																	
☐ Recuadro No. IV	Falta de unidad de invención																	
☒ Recuadro No. V	Declaración motivada de conformidad con el Artículo 35(2), en relación con la novedad, el nivel inventivo o la aplicabilidad industrial; citas y explicaciones que respaldan dicha declaración																	
☐ Recuadro No. VI	Ciertos documentos citados																	
☐ Recuadro No. VII	Ciertos defectos en la solicitud internacional																	
☒ Recuadro No. VIII	Ciertas observaciones sobre la solicitud internacional																	
Fecha de presentación de la demanda 14/02/2022	Fecha de finalización del presente informe 01/08/2022																	
Nombre y dirección postal de la ISA/BR INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Mayrink Veiga n° 9, 6° andar cep: 20090-910, Centro - Rio de Janeiro/RJ Número de fax: +55 21 3037-3663	Funcionario autorizado Luiz Eduardo Kaercher Teléfono No. +55 21 3037-3686/3742																	

**INFORME PRELIMINAR INTERNACIONAL SOBRE
PATENTABILIDAD**

No. de solicitud internacional
PCT/BR2021/050158

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 del idioma original al siguiente idioma _____, que es el de una traducción proporcionada a los fines de:
 - ☐ búsqueda internacional (según Normas 12.3.(a) y 23.1.(b))
 - ☐ publicación de la solicitud internacional (según Norma 12.4.(a))
 - ☐ examen preliminar internacional (según Normas 55.2.(a) y/o 55.3.(a) y (b))

2. Por lo que respecta a los **elementos** de la solicitud internacional, esta opinión se 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 solicitud internacional tal y como fue inicialmente presentada/enviada
- ☒ la descripción: páginas **1 a 9**, tal como se presentaron/enviaron inicialmente
Páginas , recibidas por esta Administración en fecha
Páginas , recibidas por esta Administración en fecha
- ☒ las reivindicaciones: números , tal como se presentaron/enviaron inicialmente
números , modificadas (acompañadas de una declaración) según el Artículo 19
números **1 a 7**, recibidas por esta Administración el **14/02/2022**
- ☒ los dibujos: páginas **1 a 3**, tal como se presentaron/enviaron inicialmente
páginas , recibidas por esta Administración en fecha
páginas , recibidas por esta Administración en fecha
- ☐ una lista de secuencias - ver Recuadro Suplementario relativo a listas de secuencias.

3. ☒ Las modificaciones ha ocasionado la anulación de:

- ☐ la descripción, páginas
- ☒ las reivindicaciones, Nos. **8**
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (*precisar*):

4. ☐ Esta opinión se ha establecido como si (algunas de) las modificaciones listadas más abajo no se hubieran realizado ya que, o bien se considera que van más allá de la divulgación de la invención tal como fue presentada, o bien no se acompañaron de una carta indicando la base para las modificaciones en la solicitud tal y como se presentó, como se indica en el Recuadro Suplementario (Norma 70.2.(c) y (c-bis)).

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (*precisar*):

5. ☐ Esta opinión se ha establecido:

- ☐ tomando en consideración **la rectificación de un error evidente** autorizado por o notificado a esta Administración según la Norma 91 (Normas 66.1.(d-bis) y 70.2.(e)).
- ☐ sin tomar en consideración **la rectificación de un error evidente** autorizado por o notificado a esta Administración según la Norma 91 (Normas 66.4bis y 70.2.(e)).

6. Por lo que respecta a las búsquedas complementarias (Normas 66.1ter y 70.2.(f):

- ☒ esta Administración ha realizado una búsqueda complementaria el 27 de octubre de 2021
- ☐ se han recuperado documentos adicionales durante la búsqueda complementaria
- ☐ esta Administración no ha realizado búsqueda complementaria por considerar que no sería de utilidad.

7. ☐ El(los) informe(s) de búsqueda internacional suplementario(s) emitido(s) por la(s) Administración(es) _____ ha(n) sido recibido(s) y tomados(s) en consideración para establecer esta opinión (Norma 45bis.8.(b) y (c)).

** Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".*

**INFORME PRELIMINAR INTERNACIONAL SOBRE
PATENTABILIDAD**

No. de solicitud internacional
PCT/BR2021/050158

Recuadro III.	No se establece opinión con respecto a la novedad, el nivel inventivo y la aplicabilidad industrial
No se ha examinado la cuestión de saber si el objeto de la invención reivindicada parece ser nuevo, si implica una actividad inventiva (no ser evidente), o si es susceptible de aplicación industrial, por lo que respecta: ☐ al conjunto de la solicitud internacional, ☒ a las reivindicaciones Nos. 5 y 6 debido a que: ☒ la solicitud internacional o las reivindicaciones Nos. 5 y 6 en cuestión, se refieren al objeto siguiente, respecto del cual la Administración no está obligada a efectuar un examen preliminar internacional (precisar): Método para el tratamiento del cuerpo humano o animal mediante terapia según el artículo 17(2)(a)(i) y Regla 67.1 (iv) (PCT). ☐ la descripción, las reivindicaciones o los dibujos (indíquense cuáles a continuación) o las reivindicaciones Nos. _____ en cuestión, no son claros, de manera que no es posible formular una opinión significativa (precisar): ☐ las reivindicaciones, o las reivindicaciones Nos. _____ en cuestión, no están fundadas adecuadamente en la descripción, por lo que es imposible formular una opinión significativa (precisar): ☒ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos. 5 y 6 ☐ no fue posible formular una opinión significativa sin la lista de secuencias; el solicitante en el plazo previsto no: ☐ presentó una lista de secuencias en forma de archivo de texto del Anexo C/ST.25, y dicha lista no estaba disponible para la Administración encargada del examen preliminar internacional en la forma y manera aceptables para ella; o la lista de secuencias facilitada no cumplía con la norma prevista en el Anexo C de las Instrucciones Administrativas. ☐ presentó una lista de secuencias en papel o en forma de archivo de imagen que cumpla con el estándar previsto en el Anexo C de las Instrucciones Administrativas, y dicha lista no estaba disponible para la Administración encargada del examen preliminar internacional en la forma y manera aceptables para ella; o la lista de secuencias facilitada no cumplía con la norma prevista en el Anexo C de las Instrucciones Administrativas. ☐ pagó la tasa por presentación tardía de una lista de secuencias en respuesta a un requerimiento según las Reglas 13ter.1.a) y 13ter.2 ☐ ver Recuadro Suplementario para más detalles.	

**INFORME PRELIMINAR INTERNACIONAL SOBRE
PATENTABILIDAD**

No. de solicitud internacional
PCT/BR2021/050158

Recuadro V. Declaración motivada según el Artículo 35.(2) sobre la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones en apoyo de esta declaración

1. Declaración

Novedad	Reivindicaciones 7	SÍ
	Reivindicaciones 1 a 4	NO
Nivel inventivo	Reivindicaciones -----	SÍ
	Reivindicaciones 1 a 4 y 7	NO
Aplicación industrial	Reivindicaciones 1 a 4 y 7	SÍ
	Reivindicaciones -----	NO

2. Citas y explicaciones (regla 70.7):

1) Documentos citados: se consideraron relevantes D1: WO 2018076090 A1 y D2: Angeliki Karamitri y Ralf Jockers, *Melatonin in type 2 diabetes mellitus and obesity, Nature Reviews I Endocrinology*, volumen 15, Febrero 2019, 105.

2) El objeto reivindicado es un compuesto de bencimidazol específico de fórmula I para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica.

3) El solicitante presentó argumentos para definir mejor la invención y aclarar las diferencias entre la materia reivindicada en la presente solicitud y el estado de la técnica citado.

Según el Solicitante, (...) *las enseñanzas de los documentos del estado de la técnica mencionados por el Examinador no se refieren a este uso específico y tampoco orientan a un experto en la materia a desarrollar la presente invención, es decir, a utilizar específicamente el compuesto de fórmula para la materia reivindicada en la presente solicitud.*

(...) *nunca se han desarrollado fármacos dirigidos a receptores de melatonina específicos (MT1 o MT2) en tejidos periféricos. Sin embargo, los inventores de la presente invención pudieron desarrollar sorprendentemente que el compuesto específico de fórmula I: i) actúa como un agonista melatonérgico con mayor potencia en el receptor MT1 que en el receptor MT2 (véase Tabla 1 en la memoria descriptiva) y ii) muestra una exposición periférica más alta que la central, es decir, una relación cerebro-plasma baja. (véase Tabla 2 en la memoria descriptiva), actuando así preferentemente sobre los tejidos periféricos.*

(...) *En el Ejemplo 1, por ejemplo, los efectos del derivado de bencimidazol de fórmula I, un agonista más potente en MT1 que en MT2, se compararon con N-[3-(5-Cloro-2-etoxi-6-metoxi-benzoimidazol-1-il)-propil]-acetamida (estructura representada a continuación - fórmula II), un agonista melatonérgico con mayor potencia en los receptores MT2 que en los receptores MT1 (es decir, opuesto al derivado de bencimidazol de fórmula I según la presente invención), y a aquellos de dapagliflozina, un inhibidor de SGLT2 que normaliza los niveles de glucosa en sangre y reduce el peso corporal en modelos DIO (Millar Pet al. (2017).*

El compuesto reivindicado en la reivindicación 1, *per se*, se describe en D1 (compuesto 143, página 74, ejemplo 22) además de ser específicamente reivindicado en la reivindicación 3 de D1. Asimismo, las composiciones reivindicadas en las reivindicaciones 2 a 4 se describen en D1 (reivindicaciones 10 y 12), por lo que las reivindicaciones 1 a 4 no están de acuerdo con el art. 33(2) y 33(3) PCT. El uso (reivindicación 7) del compuesto de Fórmula (I) en la fabricación de una composición farmacéutica para el tratamiento de la obesidad, diabetes, enfermedad del hígado graso no alcohólico y esteatohepatitis no alcohólica se considera novedoso respecto al documento D1, por lo tanto, la reivindicación 7 están de acuerdo con el art. 33(2) PCT.

Recuadro VIII. Ciertas observaciones sobre la solicitud internacional

Se hacen las siguientes observaciones sobre la claridad de las reivindicaciones, la descripción y los dibujos o sobre la cuestión de si las reivindicaciones están totalmente respaldadas por la descripción:

Según el solicitante respecto a la síntesis del compuesto de fórmula I (...) *la presente invención no se refiere ni reivindica el compuesto de fórmula I per se. Además, el proceso para obtener tal compuesto tampoco es parte de la presente invención.*

Esta Administración encargada de la búsqueda internacional no está de acuerdo, ya que se conservan las reivindicaciones del compuesto y la composición en el capítulo reivindicatorio.

Por lo tanto, no hay suficiente divulgación para la materia reivindicada en las reivindicaciones 1-4, por lo que no están de conformidad con el Artículo 5 del PCT.

Recuadro Suplementario

En caso de que **el espacio en alguno de los cuadros anteriores no sea suficiente.**

Continuación de: **Recuadro No. V**

Sin embargo, como ya se ha considerado, a lo largo de la descripción del documento D1 se revela que tales compuestos tienen afinidad por los receptores melatonérgicos y el documento D2 revela la asociación directa de estos receptores con las patologías ligadas al uso reivindicado. De esta forma, se entiende que a partir de la información divulgada en los documentos D1 y D2, un experto en la materia lograría la materia reivindicada. Así, la reivindicación 7 no se encuentra de conformidad con el art. 33(3) PCT.

4) La aplicabilidad industrial de las reivindicaciones 1 - 4 y 7 está fuera de toda duda de acuerdo con el art. 33 (4) PCT.