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54. TITULO Uso de Antagonistas del Mg²⁺ para el
Tratamiento de Erge

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71. SOLICITANTE 1. AstraZeneca AB 2. NPS Pharmaceuticals, Inc.

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22. BOGOTA, D.C., Diciembre 2, 2004

(SS)

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☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
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	Teléfono: Fax: E. Mail:		
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
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 2. Reporte internacional de búsqueda
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF MGLUR5 ANTAGONISTS FOR THE TREATMENT OF GERD

(57) Abstract: The present invention relates to the use of metabotropic glutamate receptor 5 antagonists for the inhibition of transient lower esophageal sphincter relaxations. A further aspects of the invention is directed to the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastro, esophageal reflux disease, as well as for the treatment of regurgitation and asthma.

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USE OF MGLUR5 ANTAGONISTS FOR THE TREATMENT OF GERD

Field of the invention

5 The present invention relates to the use of metabotropic glutamate receptor 5 (mGluR5) antagonists for the inhibition of transient lower esophageal sphincter relaxations. A further aspect of the invention is directed to the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastro-esophageal reflux disease, as well as for the treatment of regurgitation.

10

Background of the invention

The metabotropic glutamate receptors (mGluR) are G-protein coupled receptors that are involved in the regulation and activity of many synapses in the central nervous system (CNS). Eight metabotropic glutamate receptor subtypes have been identified and are subdivided into three groups based on sequence similarity. Group I consists of mGluR1 and mGluR5. These receptors activate phospholipase C and increase neuronal excitability. Group II, consisting of mGluR2 and mGluR3 as well as group III, consisting of mGluR4, mGluR6, mGluR7 and mGluR8 are capable of inhibiting adenylyl cyclase activity and reduce synaptic transmission. Several of the receptors also exist in various isoforms, occurring by alternative splicing (*Chen, C-Y et al., Journal of Physiology (2002), 538.3, pp. 773-786; Pin, J-P et al., European Journal of Pharmacology (1999), 375, pp. 277-294; Bräuner-Osborne, H et al. Journal of Medicinal Chemistry (2000), 43, pp. 2609-2645; Schoepp, D.D, Jane D.E. Monn J.A. Neuropharmacology (1999), 38, pp. 1431-1476*).

25

The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".

30

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend

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The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".

30 Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend

on a hypotonic lower esophageal sphincter. However, e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535*, has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal
5 in patients with GERD.

According to *Blackshaw L.A. et al., presentation at the conference Neurogastroenterology & Motility, Madison, Wisconsin, 14 November 2001*, metabotropic glutamate receptors of group II and group III, i.e. mGluR2, mGluR3, mGluR4, mGluR6, mGluR7 and mGluR8
10 may be involved in selective inhibitory modulation of peripheral mechanosensory endings.

The object of the present invention was to find a new way for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), thereby preventing reflux. More particularly the object of the invention was to find a new and improved way of treating
15 gastro-esophageal reflux disease (GERD), as well as a new and improved way for the treatment of regurgitation.

Outline of the invention

20 It has now surprisingly been found that metabotropic glutamate receptor 5 (mGluR5) antagonists are useful for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), and thus for the treatment of gastro-esophageal reflux disease (GERD).

25 Consequently, the present invention is directed to the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).

A further aspect of the invention is the use of a metabotropic glutamate receptor 5
30 antagonist for the manufacture of a medicament for the prevention of reflux.

Still a further aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment of gastro-esophageal reflux disease (GERD).

5 Effective prevention of regurgitation would be an important way of preventing, as well as curing lung disease due to aspiration of regurgitated gastric contents, and for managing failure to thrive. Thus, a further aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment of regurgitation.

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Still a further aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment or prevention of lung disease.

15 Another aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the management of failure to thrive.

Still a further aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment or prevention of asthma, such as reflux-related asthma.

20

Another aspect of the invention is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment or prevention of chronic laryngitis.

25

A further aspect of the present invention is a method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such inhibition.

30

Another aspect of the invention is a method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such prevention.

5 Still a further aspect of the invention is a method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such treatment.

10 Yet another aspect of the invention is a method for the treatment of regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such treatment.

15 Still a further aspect of the invention is a method for the treatment or prevention of asthma, such as reflux-related asthma, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such treatment.

20 Yet another aspect of the invention is a method for the treatment of chronic laryngitis, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such treatment. Still a further aspect of the invention is a method for the treatment or inhibition of lung disease, whereby a pharmaceutically and pharmacologically effective amount of a
25 metabotropic glutamate receptor 5 antagonist is administered to a subject in need of such treatment.

Still a further aspect of the invention is a method for the management of failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic
30 glutamate receptor 5 antagonist is administered to a subject in need of such treatment.

For the purpose of this invention, the term "antagonist" should be understood as including full antagonists, inverse agonists, non-competitive antagonists or competitive antagonists, as well as partial antagonists, whereby a "partial antagonist" should be understood as a compound capable of partially, but not fully, in-activating the metabotropic glutamate receptor 5.

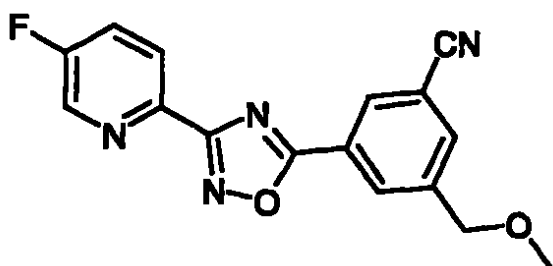
The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

The wording "reflux" is defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

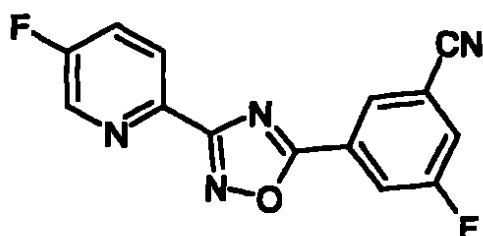
The wording "GERD", gastro-esophageal reflux disease, is defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

One example of a compound having antagonistic affinity to metabotropic glutamate receptor 5, thereby being useful in accordance with the invention, is the compound 2-methyl-6-(phenylethynyl)-pyridine (often abbreviated MPEP). MPEP is commercially available from e.g. Tocris, or may be synthesized according to well-known procedures such as disclosed by K. Sonogashira et al. in *Tetrahedron Lett. (1975), 50, 4467-4470.*

A further example of a compound having antagonistic affinity to metabotropic glutamate receptor 5, thereby being useful in accordance with the invention, is the compound 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile, having the structural formula:



Yet another example of a compound having antagonistic affinity to metabotropic glutamate receptor 5, thereby being useful in accordance with the invention, is the compound 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile, having the structural formula:



- 10 The use of pharmaceutically acceptable salts of metabotropic glutamate receptor 5 antagonists is also within the scope of the present invention. Such salts are for example salts formed with mineral acids such as hydrochloric acid; alkali metal salts such as sodium or potassium salts; or alkaline earth metal salts such as calcium or magnesium salts.
- 15 Metabotropic glutamate receptor 5 antagonists having an asymmetric carbon atom are chiral compounds, and depending on the presence of asymmetric atoms, the metabotropic glutamate receptor 5 antagonists may exist in the form of mixtures of isomers, particularly racemates, or in the form of pure isomers such as specific enantiomers. The use of optical isomers of metabotropic glutamate receptor 5 antagonists is also within the scope of the
- 20 present invention.

Pharmaceutical formulations

For clinical use, the metabotropic glutamate receptor 5 antagonists are in accordance with the present invention suitably formulated into pharmaceutical formulations for oral administration. Also rectal, parenteral or any other route of administration may be contemplated to the skilled man in the art of formulations. Thus, the metabotropic glutamate receptor 5 antagonists are formulated with at least one pharmaceutically and pharmacologically acceptable carrier or adjuvant. The carrier may be in the form of a solid, semi-solid or liquid diluent.

In the preparation of oral pharmaceutical formulations in accordance with the invention, the metabotropic glutamate receptor 5 antagonist(s) to be formulated is mixed with solid, powdered ingredients such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or compressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance(s) mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil, or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions, containing the active compound and the remainder of the formulation consisting of sugar or sugar alcohols, and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

10

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

15

In one aspect of the present invention, the metabotropic glutamate receptor 5 antagonists may be administered once or twice daily, depending on the severity of the patient's condition.

20

A typical daily dose of the metabotropic glutamate receptor 5 antagonists is from 0.1 – 100 mg per kg body weight of the subject to be treated, but this will depend on various factors such as the route of administration, the age and weight of the patient as well as of severity of the patient's condition.

25

Biological evaluation

Screening for compounds active against TLESR

- 5 Adult Labrador retrievers of both genders, trained to stand in a Pavlov sling, are used. Mucosa-to-skin esophagostomies are formed and the dogs are allowed to recover completely before any experiments are done.

Motility measurement

- 10 In brief, after fasting for approximately 17 h with free supply of water, a multilumen sleeve/sidehole assembly (Dentsleeve, Adelaide, South Australia) is introduced through the esophagostomy to measure gastric, lower esophageal sphincter (LES) and esophageal pressures. The assembly is perfused with water using a low-compliance manometric
15 perfusion pump (Dentsleeve, Adelaide, South Australia). An air-perfused tube is passed in the oral direction to measure swallows, and an antimony electrode monitored pH, 3 cm above the LES. All signals are amplified and acquired on a personal computer at 10 Hz.

- When a baseline measurement free from fasting gastric/LES phase III motor activity has
20 been obtained, placebo (0.9% NaCl) or test compound is administered intravenously (i.v., 0.5 ml/kg) in a foreleg vein. Ten min after i.v. administration, a nutrient meal (10% peptone, 5% D-glucose, 5% Intralipid, pH 3.0) is infused into the stomach through the central lumen of the assembly at 100 ml/min to a final volume of 30 ml/kg. Immediately following the meal, air is insufflated at 40 ml/min. In an alternative model (Barostat
25 model), the infusion of the nutrient meal is followed by air infusion at a rate of 500 ml/min until a intragastric pressure of 10 ± 1 mmHg is obtained. The pressure is then maintained at this level throughout the experiment using the infusion pump for further air infusion or for venting air from the stomach. The experimental time from start of nutrient infusion to end of air insufflation is 45 min. The procedure has been validated as a reliable means of
30 triggering TLESRs.

TLESRs is defined as a decrease in lower esophageal sphincter pressure (with reference to intragastric pressure) at a rate of >1 mmHg/s. The relaxation should not be preceded by a pharyngeal signal ≤ 2 s before its onset in which case the relaxation is classified as swallow-induced. The pressure difference between the LES and the stomach should be less than
5 2 mmHg, and the duration of the complete relaxation longer than 1 s.

EXAMPLES

Example 1

- 10 2-Methyl-6-(phenylethynyl)-pyridine (MPEP) was prepared according to the procedure described by K. Sonogashira et al. in *Tetrahedron Lett.* (1975), 50, 4467-4470. After purification by column chromatography (SiO_2), the hydrochloride salt (the hydrochloride salt of 2-methyl-6-(phenylethynyl)-pyridine is also commercially available from e.g. Tocris) was prepared by introducing HCl(g) to an ice-cooled Et_2O -solution of the product.
- 15 The hydrochloride salt of MPEP was tested on adult Labrador retrievers of both genders in accordance with the test model described above.

Inhibition of the number of TLESRs was calculated with regard to the five preceding control experiments for each dog, and the results as set out in Tables 1.1 and 1.2 below
20 were achieved.

Table 1.1 – Standard model

Compound	DOSE [$\mu\text{mol/kg}$]	% INHIBITION $\pm$ SEM (N)
MPEP	1.4	30 ± 5 (4)
MPEP	4.3	57 ± 8 (4)
MPEP	8.7	59 ± 11 (3)

N = number of dogs tested SEM = standard error of mean

Table 1.2 – Standard model

Compound	DOSE [$\mu\text{mol/kg/h}$] <i>infusion during 60 min</i>	% INHIBITION $\pm$ SEM (N)
MPEP	4	32 ± 13 (4)
MPEP	6	43 ± 3 (2)

5 N = number of dogs tested SEM = standard error of mean

EXAMPLE 2

3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile was prepared according to the procedure described in WO 02/068417. 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile was tested on adult Labrador retrievers of both genders in accordance with the barostat model described above.

Table 2.1 – Barostat model

Compound	DOSE [μ mol/kg/h] <i>infusion during 55 min</i>	% INHIBITION $\pm$ SEM (N)
3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile	1.1	58 $\pm$ 11 (4)
3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile	2.2	83 $\pm$ 17 (2)

N = number of dogs tested SEM = standard error of mean

EXAMPLE 3

3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile was prepared according to the procedure described in WO 01/12627. 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile was tested on adult Labrador retrievers of both genders in accordance with the barostat model described above.

Table 3.1 – Barostat model

Compound	DOSE [μ mol/kg/h] <i>infusion during 60 min</i>	% INHIBITION $\pm$ SEM (N)
3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile	1	70 $\pm$ 4 (3)

N = number of dogs tested SEM = standard error of mean

The results shown in the Examples above, support that metabotropic glutamate receptor 5 antagonists are useful for the inhibition of TLESRs, and thus for the treatment of GERD.

Claims

1. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament
5 for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).
2. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of gastro-esophageal reflux disease (GERD).
- 10 3. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the prevention of reflux.
- 15 4. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, regurgitation.
- 20 5. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, asthma.
6. Use according to claim 5, wherein the asthma is reflux-related asthma.
- 25 7. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, chronic laryngitis.

8. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, lung disease.
- 5 9. Use of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for managing failure to thrive.
- 10 10. Use according to any one of the preceding claims, wherein the metabotropic glutamate receptor 5 antagonist is 2-methyl-6-(phenylethynyl)-pyridine.
11. Use according to claim 10, wherein the metabotropic glutamate receptor 5 antagonist is the hydrochloride salt of 2-methyl-6-(phenylethynyl)-pyridine.
- 15 12. Use according to any one of claims 1-9, wherein the metabotropic glutamate receptor antagonist is 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile.
- 20 13. Use according to any one of claims 1-9, wherein the metabotropic glutamate receptor antagonist is 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile.
- 25 14. Use according to any one of the preceding claims, wherein the daily dose of the metabotropic glutamate receptor 5 antagonist is from 0.1 – 100 mg per kg body weight of the subject to be treated.
- 30 15. A method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such inhibition.

16. A method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment.
17. A method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such prevention.
18. A method for the treatment of, or prevention of, regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.
19. A method for the prevention of, or treatment of, lung disease, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.
20. A method for managing failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such management.
21. A method for treatment or prevention of asthma, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.

22. A method according to claim 21, wherein the asthma is reflux-related asthma.
23. A method for treatment or prevention of chronic laryngitis, whereby a
5 pharmaceutically and pharmacologically effective amount of a metabotropic
glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or an
optical isomer thereof, is administered to a subject in need of such treatment or
prevention.
- 10 24. A method according to any one of claims 15-23, wherein the metabotropic
glutamate receptor 5 antagonist is 2-methyl-6-(phenylethynyl)-pyridine.
25. A method according to claim 24, wherein the metabotropic glutamate receptor 5
antagonist is the hydrochloride salt of 2-methyl-6-(phenylethynyl)-pyridine.
- 15 26. A method according to any one of claims 15-23, wherein the metabotropic
glutamate receptor 5 antagonist is 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-
yl]-5-(methoxymethyl)benzonitrile.
- 20 27. A method according to any one of claims 15-23, wherein the metabotropic
glutamate receptor 5 antagonist is 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-
oxadiazol-5-yl]benzonitrile.
- 25 28. A method according to any one of claims 15-27, wherein the daily dose of the
metabotropic glutamate receptor 5 antagonist is from 0.1 – 100 mg per kg body
weight of the subject to be treated.

USO DE ANTAGONISTAS DEL MGLUR5 PARA EL TRATAMIENTO DE ERGE

Resumen: La presente invención describe el uso de antagonistas del receptor 5 metabotrópico de glutamato para la inhibición de relajaciones transitorias del esfínter esofágico inferior. Un aspecto adicional de esta invención está enfocado al uso de los antagonistas del receptor 5 metabotrópico de glutamato para el tratamiento de la enfermedad de reflujo gastro-esofágico, así como para el tratamiento de la regurgitación y del asma.

Campo de la Invención

La presente invención describe el uso de antagonistas del receptor 5 metabotrópico de glutamato (R5mGlu) para la inhibición de relajaciones transitorias del esfínter esofágico inferior. Un aspecto adicional de esta invención está enfocado al uso de los antagonistas del receptor 5 metabotrópico de glutamato para el tratamiento de la enfermedad de reflujo gastro-esofágico, así como para el tratamiento de la regurgitación.

Antecedentes de la Invención

Los receptores metabotrópicos de glutamato (mGluR) son receptores proteínas-G acopladas que están involucrados en la regulación y la actividad de muchas sinapsis en el sistema nervioso central (SNC). Se han identificado ocho subtipos de receptores metabotrópicos de glutamato y se subdividen en tres grupos con base en la semejanza

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de la secuencia. El grupo I consta de mGluR1 y mGluR5. Estos receptores activan la fosfolipasa C e incrementan la excitabilidad neuronal. El grupo II que está formado por mGluR2 y mGluR3, así como el grupo III, conformado por mGluR4, mGluR6, mGluR7 y mGluR8, son capaces de inhibir la actividad de la adenilil ciclasa y reducir la transmisión sináptica. Varios de los receptores también existen en las varias isoformas, presentándose por empalmes alternativos (*Chen, C-Y et al., Journal of Physiology (2002), 538. 3, pp.773-786*, *Pin, J-P et al., European Journal of Pharmacology (1999), 375, pp.277-294*; *Brduner-Osborne, H et al. Journal of Medicinal Chemistry (2000), 43, pp. 2609-2645*; *Schoepp, D. D, Ja7ze D. E. Monn J. A. Neuropharmacology (1999), 38, pp.1431-1476*).

El esfínter esofágico inferior (EEI) es propenso a relajarse de forma intermitente. Como consecuencia de esto, puede pasar fluido del estómago al esófago puesto que en estas circunstancias la barrera mecánica es temporalmente perdida, una situación que en adelante será referida como "reflujo".

La enfermedad de reflujo Gastro-Esofágico (ERGE) es la enfermedad más frecuente en el tracto gastrointestinal superior. La farmacoterapia actual tiene como objetivo reducir la secreción de ácidos gástricos o neutralizar el ácido en el esófago. Se ha considerado que el principal mecanismo causante del reflujo obedece a un esfínter esofágico inferior hipotónico. Sin embargo, e. g. *Holloway y Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535*, han demostrado que la mayoría de los episodios de reflujo ocurren durante las relajaciones transitorias del esfínter esofágico inferior (RTEEs), es

decir relajaciones que no son provocadas por la ingestión. También se ha demostrado que la secreción de ácidos gástricos generalmente es normal en pacientes con ERGE.

De acuerdo con *Blackshaw L. A. et al., Presentation at the conference Neurogastroeszterology and Motility, Madison, Wisconsin, 14 Novenzber 2001*, los receptores metabotrópicos de glutamato de los grupos II y III, es decir mGluR2, mGluR3, mGluR4, mGluR6, mGluR7 y mGluR8 pueden estar involucrados en la modulación inhibitoria selectiva de las terminaciones periféricas mecano sensoriales.

El objetivo de la presente invención fue encontrar una nueva opción para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs), y por medio de esto prevenir el reflujo. De forma más particular el objetivo de la invención fue encontrar una opción nueva y mejorada para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE), así como también una opción nueva y mejorada para el tratamiento de la regurgitación.

Descripción de la Invención

Ahora se ha encontrado de forma sorpresiva que los antagonistas del receptor 5 metabotrópico de glutamato (mGluR5) son útiles para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs) y por lo tanto para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE).

En consecuencia, la presente invención está enfocada al uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs).

Un aspecto adicional de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para la prevención de reflujo.

Incluso otro aspecto adicional de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE).

La prevención eficaz de la regurgitación podría ser una manera de prevención, así como de curación de una enfermedad pulmonar causada por la aspiración de contenidos gástricos regurgitados y para el manejo del retraso en el crecimiento. De esta forma, un aspecto adicional de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para el tratamiento de la regurgitación.

Incluso otro aspecto adicional de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para el tratamiento o prevención de una enfermedad pulmonar.

Otro aspecto de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para manejar el retraso en el crecimiento.

Incluso otro aspecto adicional de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para el tratamiento o prevención de asma, tal como asma relacionada con reflujo.

Otro aspecto de la invención es el uso de un antagonista del receptor 5 metabotrópico de glutamato para la manufactura de un medicamento para el tratamiento o prevención de laringitis crónica.

Un aspecto adicional de la presente invención es un método para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs), por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal inhibición.

Otro aspecto de la invención es un método para la prevención del reflujo, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal prevención.

Incluso otro aspecto adicional de la invención es un método para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE), por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Todavía otro aspecto de la invención es un método para el tratamiento de la regurgitación, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Incluso otro aspecto de la invención es un método para el tratamiento o prevención de asma, tal como asma relacionada con reflujo, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Todavía otro aspecto de la invención es un método para el tratamiento de laringitis crónica, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Incluso otro aspecto de la invención es un método para el tratamiento o inhibición de una enfermedad pulmonar, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Incluso otro aspecto de la invención es un método para el tratamiento de retraso en crecimiento, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato es administrado a un sujeto que necesite de tal tratamiento.

Para los propósitos de esta invención, debe entenderse que el término "antagonista" incluye antagonistas totales, antagonistas inversos, antagonistas no-competitivos o antagonistas competitivos, así como antagonistas parciales, de modo que un "antagonista parcial" debe ser entendido como un compuesto capaz de dejar parcialmente, pero no totalmente, inactivo el receptor 5 metabotrópico de glutamato.

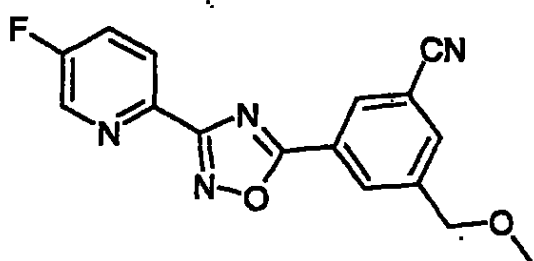
El término "RTEEI", relajaciones transitorias del esfínter esofágico inferior, es definido aquí de acuerdo con *Mittal, R.K., Holloway, R. H., Penagini, R., Blackshaw, L.A., Dent, J., 1995 ; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

El término "reflujo" es definido como un fluido del estómago capaz de pasar hasta el esófago, puesto que en estas circunstancias la barrera mecánica es temporalmente perdida.

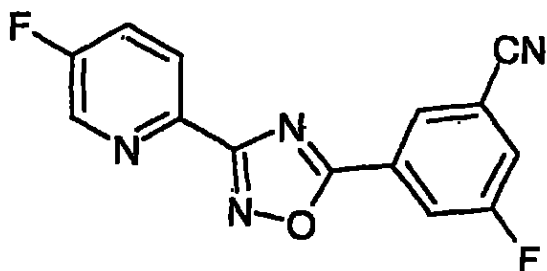
El término "ERGE", enfermedad de reflujo gastro-esofágico (ERGE) está definido de acuerdo con *van Heerwarden, M.A., Smout A. J. P. M., 2000 ; Diagnosis of reflux disease. Bailliere's Clifz. Gastroenterol. 14, pp. 759-774.*

Un ejemplo de un compuesto que tiene afinidad antagónica por el receptor 5 metabotrópico de glutamato, y por lo tanto es útil de acuerdo con la invención, es el compuesto 2-metil-6-(feniletinil)-piridina (frecuentemente abreviado como MPEP). MPEP está disponible comercialmente de e. g. Tocris, o puede ser sintetizado de acuerdo con procedimientos bastante conocidos en la literatura como tales como el divulgado por *K. Sonogashira et al. en Tetrahedron Lett. (1975), 50, 4467-4470.*

Un ejemplo más de un compuesto que tiene afinidad antagónica por el receptor 5 metabotrópico de glutamato, y por lo tanto es útil de acuerdo con la invención, es el compuesto 3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo, que tiene la fórmula estructural:



Aún otro ejemplo de un compuesto que tiene afinidad antagónica por el receptor 5 metabotrópico de glutamato, y por lo tanto es útil de acuerdo con la invención, es el compuesto 3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo, que tiene la fórmula estructural:



El uso de sales farmacéuticamente aceptables de los antagonistas del receptor 5 metabotrópico de glutamato también está incluido dentro del alcance de la presente invención. Tales sales son por ejemplo sales formadas con ácidos minerales tales como ácido clorhídrico; sales de metales alcalinos tales como sales de sodio o potasio; o sales de metales alcalinotérreos tales como sales de calcio y magnesio.

Los antagonistas del receptor 5 metabotrópico de glutamato que tienen un átomo de carbono asimétrico son compuestos quirales, y dependiendo de la presencia de átomos asimétricos, los antagonistas del receptor 5 metabotrópico de glutamato pueden existir en la forma de mezclas de isómeros, particularmente racematos, o en la forma de isómeros puros tales como enantiómeros específicos. El uso de isómeros ópticos de los antagonistas del receptor 5 metabotrópico de glutamato está también dentro del alcance de la presente invención.

Formulaciones Farmacéuticas

Para el uso clínico, los antagonistas del receptor 5 metabotrópico de glutamato de acuerdo con la presente invención son formulados de manera adecuada e incluidos en formulaciones farmacéuticas para su administración oral. Adicionalmente rectal, parenteral o cualquier otra ruta de administración puede ser contemplada por la persona con suficiente entrenamiento en el arte de las formulaciones. Así, los antagonistas del receptor 5 metabotrópico de glutamato son formulados con al menos un vehículo o adyuvante farmacéuticamente y farmacológicamente aceptable.

En la preparación de formulaciones farmacéuticas orales de acuerdo con la invención, el(los) antagonista(s) del receptor 5 metabotrópico de glutamato que será formulado es mezclado con ingredientes sólidos en polvo tales como lactosa, sacarosa, sorbitol, manitol, almidón, amilopectina, derivados de celulosa, gelatina u otros ingredientes adecuados, tales como agentes dispersantes y agentes lubricantes tales como estearato de magnesio, estearato de calcio, estearil fumarato de sodio y ceras de polietilenglicol. La mezcla es procesada entonces en forma de gránulos o comprimida en forma de tabletas.

Capsulas de gelatina blanda pueden ser preparadas usando cápsulas que contengan una mezcla del compuesto o los compuestos de la invención, aceite vegetal, grasa u

otro vehículo conveniente para las cápsulas de gelatina blanda. Cápsulas de gelatina dura pueden contener el compuesto activo combinado con ingredientes sólidos en polvo tales como lactosa, sacarosa, sorbitol, manitol, almidón de papa, almidón de maíz, amilopectina, derivados de celulosa o gelatina.

Las unidades de dosificación para la administración rectal pueden ser preparadas (i) en forma de supositorios los cuales contienen la(s) sustancia(s) activa(s) mezclada(s) con una base grasa neutra; (ii) en forma de una capsula de gelatina de uso rectal la cual contiene la sustancia activa mezclada con un aceite vegetal, un aceite parafínico u otro vehículo conveniente para cápsulas de gelatina de uso rectal; (iii) en forma de un micro enema preparado; (iv) en forma de una formulación de micro enema seco que debe ser reconstituido en el solvente adecuado justo antes de su administración.

Las preparaciones líquidas para administración oral pueden ser preparadas en forma de jarabes o suspensiones, e.g. soluciones o suspensiones, que contengan el compuesto activo y en donde el resto de la formulación consista de azúcar o alcoholes de azúcar, y una mezcla de etanol, agua, glicerol, propilenglicol y polietilenglicol. Si se desea tales preparaciones líquidas pueden contener agentes colorantes, agentes saborizantes, sacarina y carboximetilcelulosa u otro agente espesante. Las preparaciones líquidas para administración oral también pueden ser preparadas en forma de un polvo seco que puede ser reconstituido con el solvente adecuado antes de su uso.

Soluciones para administración parenteral pueden ser preparadas como una solución de un compuesto de la presente invención en un solvente farmacéuticamente aceptable. Estas soluciones pueden contener también ingredientes estabilizantes y/o ingredientes amortiguadores de pH y son suministradas en dosis individuales en forma de ampollitas o viales. Las soluciones para administración parenteral también pueden ser preparadas como una formulación seca que será reconstituida con un solvente conveniente en cualquier momento que se requiera antes de su uso.

En un aspecto de la presente invención, los antagonistas del receptor 5 metabotrópico de glutamato pueden ser administrados una o dos veces al día, dependiendo de la gravedad de la condición del paciente.

Una dosis diaria típica de los antagonistas del receptor 5 metabotrópico de glutamato se encuentra en el intervalo de 0.1-100 mg por Kg de peso corporal de el sujeto a ser tratado, pero está dependerá de varios factores tales como la ruta de administración, la edad y el peso del paciente así como la gravedad de la condición del paciente.

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Evaluación Biológica

Investigación de los compuestos con actividad en contra de RTEEI

Son usados, perros Labrador Retriever de ambos géneros, entrenados para permanecer en un amés de Pavlov. Esofagostomías mucosa-a-piel son conformadas y se permite que los perros se recuperen totalmente antes de que cualquier experimento sea realizado.

Medidas de Motilidad

En resumen, después de ayunar por aproximadamente 17h con libre suministro de agua, un montaje multilumen de introductor/abertura lateral (Dentsleeve, Adelaida, Australia) es introducido a través de la esofagostomía para medir la presión gástrica, la presión del esfínter esofágico inferior (EEI) y la presión esofágica. El montaje es inundado con agua usando una bomba manométrica de perfusión de baja-elasticidad (Dentsleeve, Adelaida, Australia). Un tubo inundado con aire es pasado en dirección oral para medir la ingestión, y se midió el pH con un electrodo del antimonio, a 3 centímetros por encima del EEI. Todas las señales son amplificadas y recibidas en un computador a 10 hertzios.

Cuando una medida de línea base libre de actividad motora de la fase III gástrico/EEI del ayuno ha sido obtenida, el placebo (0.9% NaCl) o el compuesto a ensayar es administrado por vía intravenosa (i.v., 0.5 ml/kg) en una vena de la pata delantera. Diez minutos después de la administración i. v., se introduce alimento nutritivo (peptona del 10%, d-glucosa del 5%, el 5% Intralípido, pH 3.0) en el estómago a través del orificio central del montaje con un flujo de 100 ml/min hasta un volumen final de 30 ml/kg. Inmediatamente después de la alimentación, aire es insuflado a 40 ml/min. En un modelo alternativo (modelo a presión constante), la introducción del alimento nutritivo es seguida por la introducción de aire con un flujo de 500 ml/min hasta que se obtiene una presión intragástrica de 10 ± 1 mm Hg. La presión entonces se mantiene a este nivel a través del experimento usando la bomba de introducción para la adición de más aire o para ventear el aire del estómago. El tiempo experimental desde el inicio donde se introduce el alimento hasta el final de la adición del aire es 45 minutos. El procedimiento se ha validado como un método confiable para la activación de RTEEs.

RTEEs es definida como una disminución en la presión del esfínter esofágico inferior (en comparación con la presión gástrica) a una relación >1 mm Hg/s. Dicha relajación podría no estar precedida por un estímulo de la faringe ≤ 2 s antes de este ataque, caso en el cual la relajación es clasificada como *inducidas por ingestión*. La diferencia de presión entre el EEI y el estómago debe ser menor que 2 mm Hg y el tiempo total de la relajación debe ser mayor que 1 s.

EJEMPLOS

EJEMPLO 1

2-metil-8-(feniletinil)-piridina (MPEP) fue preparado de acuerdo con el procedimiento descrito por K. Sonogashira *et al.* en *Tetrahedron Lett.* (1975), 50, 4467-4470. Tras la purificación mediante cromatografía en columna (SiO_2), el clorhidrato (el clorhidrato de 2-metil-8-(feniletinil)-piridina también se puede adquirir comercialmente de e.g. Tocris) fue preparado mediante la introducción de HCl (g) a una disolución del producto en Et_2O enfriada con hielo. El clorhidrato de MPEP fue ensayado en perros Labrador retrievers adultos de ambos géneros de acuerdo con el modelo de ensayo descrito arriba.

La inhibición del número de RTEEs fue calculado con respecto a los cinco experimentos de control precedentes para cada perro, y fueron obtenidos los resultados que se presentan a continuación en las tablas 1.1 y 1.2.

Tabla 1.1 - Modelo Standard

Compuesto	DOSIS [$\mu\text{mol/kg/h}$]	% INHIBICIÓN $\pm$ ESM (N)
MPEP	1.4	30 $\pm$ 5 (4)
MPEP	4.3	57 $\pm$ 8 (4)
MPEP	8.7	59 $\pm$ 11 (3)

N = número de perros estudiados ESM = Error Standard de la Media

Tabla 1.2 - Modelo Standard

Compuesto	DOSIS [$\mu\text{mol/kg/h}$] <i>Infusión durante 60 min</i>	% INHIBICIÓN $\pm$ ESM (N)
MPEP	4	32 $\pm$ 13 (4)
MPEP	6	43 $\pm$ 3 (2)

N = número de perros estudiados ESM = Error Standard de la Media

EJEMPLO 2

3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo fue preparado de acuerdo con el procedimiento descrito en WO 02/088417. 3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo fue ensayado en perros Labrador Retriver adultos de ambos géneros de acuerdo con el modelo a presión constante descrito anteriormente.

Tabla 2.1 – Modelo a presión constante

Compuesto	DOSIS [$\mu\text{mol/kg/h}$] <i>Infusión durante 55 min</i>	% INHIBICIÓN $\pm$ ESM (N)
3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo	1.1	58 $\pm$ 11 (4)
3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo	2.2	83 $\pm$ 17 (2)

N = número de perros estudiados

ESM = Error Standard de la Media

EJEMPLO 3

3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo fue preparado de acuerdo con el procedimiento descrito en WO 01/12627, 3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo fue probado en perros labrador retriever adultos de ambos géneros de acuerdo con el modelo a presión constante descrito anteriormente.

Tabla 3.1 – Modelo a presión constante

Compuesto	DOSIS [$\mu\text{mol/kg/h}$] <i>Infusión durante 60 min</i>	% INHIBICIÓN $\pm$ ESM (N)
3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo	1	70 $\pm$ 4 (3)

N = número de perros estudiados ESM = Error Standard de la Media

Los resultados mostrados en los ejemplos anteriores, sustentan que los antagonistas del receptor 5 metabotrópico de glutamato son útiles para la inhibición de RTEEs, y de esta forma para el tratamiento de ERGE.

Reivindicaciones

1. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs).
2. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE).
3. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para la prevención del reflujo.
4. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el tratamiento de, o prevención de, regurgitación.

5. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el tratamiento de, o prevención de, asma.
6. El uso de acuerdo con la reivindicación 5, donde el asma es asma relacionada con reflujo.
7. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el tratamiento de, o prevención de, laringitis crónica.
8. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el tratamiento de, o prevención de, de una enfermedad pulmonar.
9. El uso de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, para la manufactura de un medicamento para el manejo del retraso en el crecimiento.

10. El uso de acuerdo con cualquiera de las reivindicaciones precedentes, en donde el antagonista del receptor 5 metabotrópico de glutamato es 2-metil-6-(feniletinil)-piridina.
11. El uso de acuerdo con la reivindicación 10, en donde el antagonista del receptor 5 metabotrópico de glutamato es clorhidrato de 2-metil-6-(feniletinil)-piridina.
12. El uso de acuerdo con cualquiera de las reivindicaciones 1-9, en donde el antagonista del receptor 5 metabotrópico de glutamato es 3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo.
13. El uso de acuerdo con cualquiera de las reivindicaciones 1-9, en donde el antagonista del receptor 5 metabotrópico de glutamato es 3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo.
14. El uso de acuerdo con cualquiera de las reivindicaciones precedentes, en donde la dosis diaria del antagonista del receptor 5 metabotrópico de glutamato está en el intervalo entre 0.1-100 mg por kg de peso corporal de el sujeto a ser tratado.

15. Un método para la inhibición de relajaciones transitorias del esfínter esofágico inferior (RTEEs), por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal inhibición.

16. Un método para el tratamiento de la enfermedad de reflujo gastro-esofágico (ERGE), por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal tratamiento.

17. Un método para la prevención del reflujo, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal prevención.

18. Un método para el tratamiento de, o prevención de, la regurgitación, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal

farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal tratamiento o prevención.

19. Un método para la prevención de, o tratamiento de, una enfermedad pulmonar, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal tratamiento o prevención.

20. Un método para el manejo del retraso en el crecimiento, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal manejo.

21. Un método para el tratamiento o prevención del asma, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal tratamiento o prevención.

22. Un método de acuerdo con la reivindicación 21, en donde el asma es asma relacionada con reflujo.

23. Un método para el tratamiento o prevención de la laringitis crónica, por medio del cual una cantidad farmacéuticamente y farmacológicamente efectiva de un antagonista del receptor 5 metabotrópico de glutamato, o una sal farmacéuticamente aceptable o un isómero óptico de este, es administrada a un sujeto en necesidad de tal tratamiento o prevención.

24. Un método de acuerdo con las reivindicaciones 15-23, en donde el antagonista del receptor 5 metabotrópico de glutamato es 2-metil-6-(feniletinil)-piridina.

25. Un método de acuerdo con la reivindicación 24, en donde el antagonista del receptor 5 metabotrópico de glutamato es el clorhidrato de 2-metil-6-(feniletinil)-piridina.

26. Un método de acuerdo con las reivindicaciones 15-23, en donde el antagonista del receptor 5 metabotrópico de glutamato es 3-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il]-5-(metoximetil) benzonitrilo.

27. Un método de acuerdo con las reivindicaciones 15-23, en donde el antagonista del receptor 5 metabotrópico de glutamato es 3-fluoro-5-[3-(5-fluoropiridin-2-il)-1,2,4-oxadiazol-5-il] benzonitrilo.

28. Un método de acuerdo con las reivindicaciones 15-27, en donde la dosis diaria del antagonista del receptor 5 metabotrópico de glutamato está en el intervalo entre 0.1-100 mg por kg de peso corporal de el sujeto a ser tratado.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

BENT, Stephen A.
FOLEY & LARDNER
Washington Harbour
3000 K Street N.W., Suite 500
Washington, D.C. 20007-5143
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 30/01/2004

Applicant's or agent's file reference
085747-0243

IMPORTANT NOTIFICATION

International application No.
PCT/US03/16223

International filing date (day/month/year)
19/06/2003

Priority date (day/month/year)
20/06/2002

Applicant

ASTRAZENECA AB et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

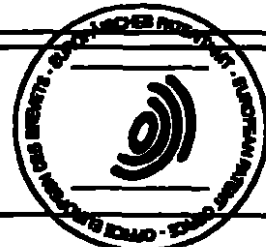
Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epcou d
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Authorized officer

FERRO VASCONCELOS M
Tel. (+49-89) 2399 2828



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 085747-0243	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/16223	International filing date (day/month/year) 19/06/2003	Priority date (day/month/year) 20/06/2002
International Patent Classification (IPC) or national classification and IPC A61K31/44		
Applicant ASTRAZENECA AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

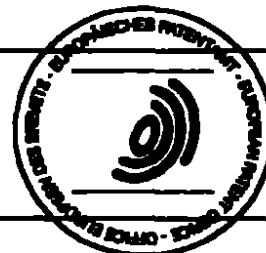
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 24/12/2003	Date of completion of this report 27/01/2004
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer SEEGERT X Tel. (+49-89) 2399 2828



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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/US03/16223

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 68.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:
IPEA/EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 085747-0243	
International application No. PCT/US03/16223	International filing date (day/month/year) (19/06/03) 19 June 2003	(Earliest) Priority date (day/month/year) (20/06/02) 20 June 2003	
Title of invention: USE OF MGLURS ANTAGONISTS FOR THE TREATMENT OF GERD			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB R & D Headquarters Global Intellectual Property S-151 85 Sodertalje SWEDEN		Telephone No.:	
		Facsimile No.:	
		Teleprinter No.:	
		Applicant's registration No. with the Office:	
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) NPS Pharmaceuticals, Inc. 420 Chipeta Way, Suite 420 Salt Lake City, UT 84108 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LEHMANN, Anders Borghamnag. 14 S-421 66 V. Frölunda SWEDEN			
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
☒ Further applicants are indicated on a continuation sheet.			

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International application No.
PCT/US03/16223

Continuation of Box No. II APPLICANT(S)	
<i>If none of the following sub-items is used, this sheet is not to be included in the demand.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
MATTSSON, Jan Kullaviksvägen 137 429333 Kullavik SWEDEN	
State (i.e. country) of nationality: SE	State (i.e. country) of residence: SE
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (i.e. country) of nationality:	State (i.e. country) of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (i.e. country) of nationality:	State (i.e. country) of residence:
[] Further applicants are indicated on a continuation sheet	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address:
BENT, Stephen A.
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
UNITED STATES OF AMERICA

Telephone No.:
(202) 672-5404

Facsimile No.:
(202) 672-5399

Teleprinter No.:

Agent's registration No. with the Office:
29,768

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:
☒ the international application as originally filed
the description ☒ as originally filed
☐ as amended under Article 34
the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
the drawings ☐ as originally filed
☐ as amended under Article 34
 2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
 3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)
- * Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English.....

- ☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)
excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|----|---|---|--------|
| 1. | translation of international application | : | sheets |
| 2. | amendments under Article 34 | : | sheets |
| 3. | copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. | copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. | letter | : | sheets |
| 6. | other (specify): | : | sheets |

For International Preliminary
Examining Authority use only

received not received

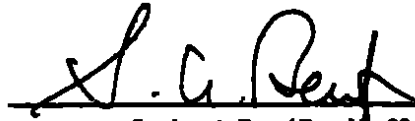
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☒ other (specify): Check to Follow via DHL Courier |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


Stephen A. Bent (Reg. No. 29,768)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

**NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE**

(PCT Rule 20.5(c))

To:
STEPHEN A. BENT
FOLEY & LARDNER
WASHINGTON HARBOUR
3000 K STREET, N.W., SUITE 500
WASHINGTON, DISTRICT OF COLUMBIA
20007-5101

Date of mailing (day/month/year) 03 Jul 2003

Applicant's or agent's file reference 085747-0243	IMPORTANT NOTIFICATION
---	-------------------------------

International application No. PCT/US03/16223	International filing date (day/month/year) 19 Jun 2003	Priority date (day/month/year) 20 Jun 2002
--	--	--

Applicant ASTRAZENECA AB

Title of the invention USE OF MGLUR5 ANTAGONISTS FOR THE TREATMENT OF GERD
--

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- ☒ was transmitted to the International Bureau on 03 Jul 2003
- ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:
- ☐ because the necessary national security clearance has not yet been obtained.
- ☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION

Completed by: KD

- ☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.
- ☐ License for foreign transmittal not required. 37 CFR 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).
- ☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 28 Jun 2003 :
☐ 37 CFR 5.15(a)
☒ 37 CFR 5.15(b)
(date)

Name and mailing address of the receiving Office
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 703-305-3230

Authorized officer
Kareem Duncan
Telephone No. (703) 305-3885

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

085747-0243

Box No. I TITLE OF INVENTION: **USE OF MGLURS ANTAGONISTS FOR THE TREATMENT OF GERD**Box No. II APPLICANT ☐ This person is also inventor.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

AstraZeneca AB
R & D Headquarters
Global Intellectual Property
S-151 85 Sodertalje
SWEDEN

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality: SE

State (that is, country) of residence: SE

This person is applicant
for the purposes of:☐all designated
States☒all designated States except
the United States of America☐the United States
of America only☐the States indicated in the
Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

NPS Pharmaceuticals, Inc.
420 Chipeta Way, Suite 240
Salt Lake City, UT 84108
UNITED STATES OF AMERICA

This person is:

☒

applicant only

☐

applicant and inventor

☐inventor only (If this check-box
is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant
for the purposes of:☐all designated
States☒all designated States except
the United States of America☐the United States
of America only☐the States indicated in the
Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BENT, Stephen A.
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C., 20007-5101
UNITED STATES OF AMERICA

Telephone No.
(202) 672-5404Facsimile No.
(202) 672-5399

Teleprinter No.

Agent's registration No. with the Office
29,768

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) 46	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> LEHMANN, Anders Borghamnsg. 14 S-421 66 V. Frölunda SWEDEN	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant For the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> MATTSSON, Jan Kullaviksvägen 137 429333 Kullavik SWEDEN	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant For the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant For the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant For the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

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Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
 - (vii) if, in Box No. VI, the earlier applications is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.
3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box IV

GEORGE C. BECK
 STEPHEN A. BENT
 BETH A. BURROUS
 ALAN I. CANTOR
 WILLIAM T. ELLIS
 JOHN J. FELDHAUS
 MICHAEL D. KAMINSKI
 MARY MICHELLE KILE
 KENNETH E. KROSIN
 GLENN LAW
 PETER G. MACK
 STEPHEN B. MAEBIUS
 BRIAN J. MC NAMARA
 RICHARD C. PEET
 GEORGE E. QUILLIN
 ANDREW E. RAWLINS
 BERNHARD D. SAXE
 CHARLES F. SCHILL
 RICHARD L. SCHWAAB
 MICHELE M. SIMKIN
 HAROLD C. WEGNER

Box No. VI PRIORITY CLAIM☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 20 June 2002 (20/06/02)	0201943-8	SE		
item (2)				
Item (3)				
Item (4)				
Item (5)				



Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as:

☐ all items ☐ item(1) ☐ item(2) ☐ item(3) ☐ item(4) ☐ item(5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

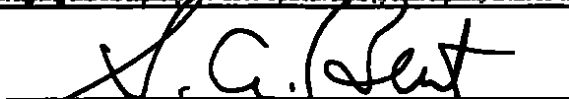
- | | | |
|--|--|---|
| ☐ Box No. VIII(i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII(ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII(iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII(iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII(v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

Box No. VII CHECK LIST; LANGUAGE OF FILING

This international application contains:	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
a) the following number of sheets is paper form:		
Request (including declaration sheets) : 6	1. ☒ fee calculation sheet	: 1
Description (excluding sequence listing part) : 13	2. ☐ original separate power of attorney	:
Claims: : 4	3. ☐ original general power of attorney	:
Abstract : 1	4. ☐ copy of general power of attorney; reference number, if any:	:
Drawings :	7. ☐ statement explaining lack of signature	:
Sub-total number of sheets : 24	6. ☒ priority document(s) identified in Box No. VI as item(s):	: 1
Sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) :	7. ☐ translation of international application into (language):	:
Total number of sheets : 24	8. ☐ separate indications concerning deposited microorganism or other biological material	:
b) Sequence listing of description filed in computer readable form	9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	:
(i) ☐ only (under Section 801(a)(i))	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	:
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))	(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
	10. ☒ other (specify): Transmittal, Postcard & Check	: 3
Figure of the drawings which should accompany the abstract: N/A	Language of filing of the international application: ENGLISH	

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


 Stephen A. Bent (Reg. No. 29,768)

For International Bureau use only		2. Drawings:
1. Date of actual receipt of the purported international application:		☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		☐ not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, HU Hungary, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, RO Republic of Romania, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|--|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SC Seychelles |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☒ DE Germany | ☒ MA Morocco | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MG Madagascar | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MN Mongolia | |
| ☒ EE Estonia | ☒ MW Malawi | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MX Mexico | ☒ VC Saint Vincent and the Grenadines |
| ☒ FI Finland | ☒ MZ Mozambique | ☒ VN Viet Nam |
| ☒ GB United Kingdom | ☒ NI Nicaragua | ☒ YU Yugoslavia |
| ☒ GD Grenada | ☒ NO Norway | ☒ ZA South Africa |
| ☒ GE Georgia | | ☒ ZM Zambia |
| ☒ GH Ghana | | ☒ ZW Zimbabwe |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ **PG** Papua New Guinea
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that these additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

BENT, Stephen. A.
Foley & Lardner
Washington Harbour
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5101
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 31 December 2003 (31.12.2003)		IMPORTANT NOTICE	
Applicant's or agent's file reference 085747-0243			
International application No. PCT/US2003/016223	International filing date (day/month/year) 19 June 2003 (19.06.2003)	Priority date (day/month/year) 20 June 2002 (20.06.2002)	
Applicant ASTRAZENECA AB et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 31 December 2003 (31.12.2003) under No. WO 2004/000318

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gijsbertus Beijer - Carlos Roy
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

15

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

FOLEY & LARDNER
Attn. Bent, Stephen A.
Washington Harbour
3000 K Street N.W., Suite 500
Washington, D.C. 20007-5101
UNITED STATES OF AMERICA

Date of mailing
(day/month/year)

03/09/2003

Applicant's or agent's file reference

085747-0243

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 03/16223

International filing date
(day/month/year)

19/06/2003

Applicant

ASTRAZENECA AB

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Eva Bohác vá

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been *in* filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 206(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 085747-0243	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 03/16223	International filing date (day/month/year) 19/06/2003	(Earliest) Priority Date (day/month/year) 20/06/2002
Applicant ASTRAZENECA AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/16223

5

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GASPARINI F ET AL: "2-METHYL-6-(PHENYLETHINYL)-PYRIDINE (MPEP), A POTENT, SELECTIVE AND SYSTEMICALLY ACTIVE MGLU5 RECEPTOR ANTAGONIST" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 10, October 1999 (1999-10), pages 1493-1503, XP001032948 ISSN: 0028-3908 the whole document --- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.*** Special categories of cited documents:****"A"** document defining the general state of the art which is not considered to be of particular relevance**"E"** earlier document but published on or after the international filing date**"L"** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)**"O"** document referring to an oral disclosure, use, exhibition or other means**"P"** document published prior to the international filing date but later than the priority date claimed**"T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention**"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone**"Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art**"A"** document member of the same patent family

Date of the actual completion of the international search

27 August 2003

Date of mailing of the international search report

03/09/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentplan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Tardif, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/16223

51

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KNÖPFEL T ET AL: "Metabotropic Glutamate Receptors: Novel targets for drug development" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 9, 28 April 1995 (1995-04-28), pages 1417-1426, XP000611483 ISSN: 0022-2623 the whole document	
A	WO 01 12627 A (SLASSI ABDELMALIK ;ISAAC METHVIN BENJAMIN (CA); STORMANN THOMAS M) 22 February 2001 (2001-02-22) cited in the application page 8, line 5,6 page 5, line 9-22	
A	US 6 117 908 A (ANDREWS PAUL L R ET AL) 12 September 2000 (2000-09-12) column 1, line 17 -column 2, line 63; claims 1-4	
A	US 5 036 057 A (MARTIN CHRISTOPHER J) 30 July 1991 (1991-07-30) claim 1	
A	WO 99 59612 A (APHTON CORP ;GEVAS PHILIP C (US); GRIMES STEPHEN (US); KARR STEPHE) 25 November 1999 (1999-11-25) page 1, line 7 -page 4, line 31; claim 1	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-9, 14-23 and 28 relate to a compound defined by reference to a desirable characteristic or property, namely a metabotropic glutamate receptor 5 antagonist.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for ~~only a very limited number of such compounds~~. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, it cannot be excluded that compounds already used for the claimed diseases possess this property.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in claims 10-13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/16223

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/16223

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0112627	A	22-02-2001	AU 6782400 A	13-03-2001
			BG 106493 A	31-01-2003
			BR 0013427 A	30-07-2002
			CA 2381975 A1	22-02-2001
			CN 1379775 T	13-11-2002
			CZ 20020599 A3	12-06-2002
			EE 200200079 A	16-06-2003
			EP 1210344 A1	05-06-2002
			HU 0202757 A2	28-12-2002
			JP 2003507378 T	25-02-2003
			NO 20020823 A	17-04-2002
			SK 2512002 A3	02-07-2002
			WO 0112627 A1	22-02-2001
			US 2003055085 A1	20-03-2003
US 6117908	A	12-09-2000	AU 714370 B2	23-12-1999
			AU 4406497 A	14-04-1998
			BR 9711400 A	17-08-1999
			CN 1237105 A , B	01-12-1999
			CZ 9900930 A3	15-09-1999
			EE 9900095 A	15-10-1999
			EP 0936906 A1	25-08-1999
			HU 9903825 A2	28-05-2001
			JP 2001501604 T	06-02-2001
			KR 2000036185 A	26-06-2000
			NO 991287 A	17-03-1999
			NZ 334495 A	29-09-2000
			NZ 504244 A	29-09-2000
			PL 332497 A1	13-09-1999
			RU 2199316 C2	27-02-2003
			WO 9811885 A1	26-03-1998
			SK 30599 A3	18-01-2000
			TR 9900591 T2	21-07-1999
			ZA 9707969 A	18-03-1998
US 5036057	A	30-07-1991	AU 594424 B2	08-03-1990
			AU 6844887 A	28-07-1987
			WO 8704077 A1	16-07-1987
			EP 0250572 A1	07-01-1988
			US 5254591 A	19-10-1993
WO 9959612	A	25-11-1999	AU 758955 B2	03-04-2003
			AU 4079899 A	06-12-1999
			CA 2332774 A1	25-11-1999
			EP 1077716 A1	28-02-2001
			JP 2002515448 T	28-05-2002
			WO 9959612 A1	25-11-1999

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

BENT, Stephen, A.
Foley & Lardner
Washington Harbour
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5101
United States of America

Date of mailing (day/month/year) 24 September 2003 (24.09.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 085747-0243	International application No. PCT/US03/16223

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

ASTRAZENECA AB et al (for all designated States except US)

LEHMANN, Anders et al (for US)

International filing date : 19 June 2003 (19.06.03)

Priority date(s) claimed : 20 June 2002 (20.06.02)

Date of receipt of the record copy
by the International Bureau : 10 July 2003 (10.07.03)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

☒ time limits for entry into the national phase - see updated important information (as of April 2002)

☐ confirmation of precautionary designations (if applicable)

☒ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Eugène POILANE (Fax 338-71-30)
Facsimile No. (41-22) 338.71.30	Telephone No. (41-22) 338 8514

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 18 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19928, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume IA, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 18-month time limit is the filing date of the earliest application whose priority is claimed.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 03/16223

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/44 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GASPARINI F ET AL: "2-METHYL-6-(PHENYLETHINYL)-PYRIDINE (MPEP), A POTENT, SELECTIVE AND SYSTEMICALLY ACTIVE MGLU5 RECEPTOR ANTAGONIST" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 10, October 1999 (1999-10), pages 1493-1503, XP001032948 ISSN: 0028-3908 the whole document — — — — — -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (see specified)
- "O" document relating to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, each combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

27 August 2003

Date of mailing of the international search report

03/09/2003

Name and mailing address of the ISA

European Patent Office, P.O. Box 1601
NL - 2200 HH Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 651 apo nl,
Fax: (+31-70) 340-3016

Authorized officer

Tard1, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/16223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KNÖPFEL T ET AL: "Metabotropic Glutamate Receptors: Novel targets for drug development" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 38, no. 9, 28 April 1995 (1995-04-28), pages 1417-1426, XP000611483 ISSN: 0022-2623 the whole document	
A	WO 01 12627 A (SLASSI ABDELMALIK ;ISAAC METHVIN BENJAMIN (CA); STORMANN THOMAS M) 22 February 2001 (2001-02-22) cited in the application page 8, line 5,6 page 5, line 9-22	
A	US 6 117 908 A (ANDREWS PAUL L R ET AL) 12 September 2000 (2000-09-12) column 1, line 17 -column 2, line 63; claims 1-4	
A	US 5 036 057 A (MARTIN CHRISTOPHER J) 30 July 1991 (1991-07-30) claim 1	
A	WO 99 59612 A (APHTON CORP ;GEVAS PHILIP C (US); GRIMES STEPHEN (US); KARR STEPHE) 25 November 1999 (1999-11-25) page 1, line 7 -page 4, line 31; claim 1	

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 03 46223

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-9, 14-23 and 28 relate to a compound defined by reference to a desirable characteristic or property, namely a metabotropic glutamate receptor 5 antagonist.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, it cannot be excluded that compounds already used for the claimed diseases possess this property.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in claims 10-13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/16223

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/16223

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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PATENT CO-OPERATION TREATY

89

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

BENT, Stephen A.
FOLEY & LARDNER
Washington Harbour
3000 K Street N.W., Suite 500
Washington, D.C. 20007-5143
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

15-01-2004

Applicant's or agent's file reference
085747-0243

IMPORTANT NOTIFICATION

International application No.
PCT/US03/16223

International filing date (day/month/year)
19/06/2003

Priority date (day/month/year)
20/06/2002

Applicant

ASTRAZENECA AB et al

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

24/12/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

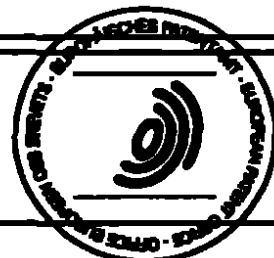


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Form PCT/IPEA/402 (April 2002; reprint January 2004)

(12/01/2004)

SUPERINDUSTRIA Y COMERCIO
Radicación : 04121729 00000000
Fecha (ADM): 2004-12-02 16:17:11
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	(✓)
MODELO DE UTILIDAD	()	(✓)
- Indicación de que se solicita la concesión de una patente.	()	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(✓)
- Descripción de la invención.	()	(✓)
- Dibujos de ser estos pertinentes. X	()	(✓)
- Comprobante de Pago de las tasas establecidas.	()	(✓)

COMPLETA ()	INCOMPLETA ()
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DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

COMPLETA ()	INCOMPLETA ()
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ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA ()	INCOMPLETA ()
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Firma Responsable: *Claudia M Neiva*

Fecha:

70
70

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

11487

Doctor(a)
DILIA MARIA RODRIGUEZ D'ALEMAN
Apoderado(a)
ASTRAZENECA AB & NPS PHARMACEUTICAL, INC.

Oficio N°

ASUNTO:

Radicación N°	04-121729
Solicitud internacional	PCT/US03/016223
Fecha inicio fase nacional	20/01/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- El solicitante deberá anexar la traducción del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante establecido, de acuerdo con la regla 4.17 51 bis PCT. (Art. 26-k) Decisión 486). Folios 51-53.
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
17 DIC. 2004

P-596

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