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① SOLICITUD DE :

☒ Patente de Invención	☐ Patente de Modelo de Utilidad
☒ Capítulo I.	☐ Capítulo II.

② SOLICITANTE (71)

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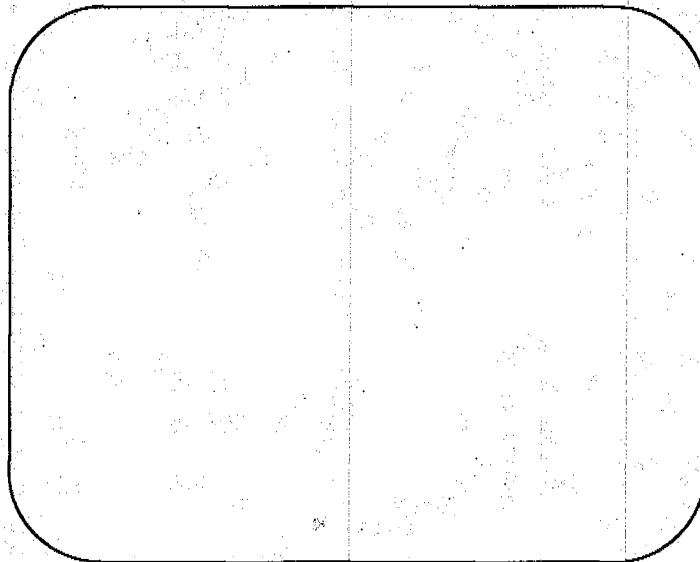
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
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- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extractos, Reporte de Búsqueda Internacional y Opinión escrita y notificación de presentación de documento de prioridad.

11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDÓÑEZ

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(54) Title: METHOD FOR THE TREATMENT OF NOISE PHOBIA IN COMPANION ANIMALS

(57) Abstract: The present invention provides a method for the non-sedative treatment of noise phobia in a companion animal, particularly a dog, which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

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(54) Title: METHOD FOR THE TREATMENT OF NOISE PHOBIA IN COMPANION ANIMALS

(57) Abstract: METHOD FOR THE TREATMENT OF NOISE PHOBIA IN COMPANION ANIMALS ABSTRACT OF THE
INVENTION The present invention provides a method for the non-sedative treatment of noise phobia in a companion animal, partic-
ularly a dog, which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-tri-
azolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

WO 2006/127574 A2

METHOD FOR THE TREATMENT OF NOISE PHOBIA IN COMPANION ANIMALS**BACKGROUND OF THE INVENTION**

5

This application claims the benefit under 35 U.S.C. §119(e) to co-pending U.S. provisional application no. 60/684669, filed May 26, 2005, which is hereby incorporated by reference in its entirety.

10 Noise and thunderstorm phobias are among the most commonly recognized disorders associated with panic or phobic responses in companion animals such as dogs, cats or horses, particularly dogs. Thunderstorms, fireworks, gunfire, car backfire, etc. frequently induce undesirable nonspecific clinical symptoms in companion animals, particularly dogs, such as salivating, defecating, urinating, destroying, escaping, hiding trembling, vocalizing and the like. Known treatments for
15 general anxiety behavior in companion animals generally involve either a long period of onset, i.e. 3-4 weeks, or if quick-acting, cause sedation and/or ataxia. However, most companion animal owners and veterinarians would prefer to treat their animals suffering from noise phobia with a method which does not promote sedation or ataxia and which is effective within an hour or two of administration.

20 Therefore, it is an object of this invention to provide a therapeutically effective method for the treatment of noise phobia in a companion animal which is non-sedative.

It is also an object of the invention to provide a veterinary composition which is useful for the treatment of noise phobia in a companion animal.

25 It is a feature of the invention that the method for the effective treatment of noise phobia in a companion animal, particularly a dog, is quick acting and does not cause ataxia.

Other objects and features of the invention will be come more apparent from the detailed description set forth herein below.

SUMMARY OF THE INVENTION

The present invention provides a method for the treatment and prevention of noise phobia in a companion animal which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

Also provided is a veterinary composition for the effective treatment of noise phobia in a companion animal.

DETAILED DESCRIPTION OF THE INVENTION

Owners of companion animals and veterinarians strive to find means to control noise phobia in their animals such as dogs, cats and horses, particularly dogs. Noise phobia behaviors may include hiding, scanning, urinating, defecating, panting, chewing, pacing, escaping, trembling, vocalizing and the like. Known therapies used for noise phobia include off-label therapies such as clomipramine, amitriptyline and buspirone which can take more than 3-4 weeks before an effect is apparent, or the use of benzodiazepines, acepromazine or antidepressants which act more quickly but often cause sedation and ataxia.

Surprisingly, it has now been found that N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide (acetamide) or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (carbonitrile) is useful for the therapeutic treatment and prevention of noise phobia in a companion animal without causing sedation or ataxia and with a shortened period of onset. Accordingly the present invention provides a method for the treatment and prevention of noise phobia in a companion animal which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile. Advantageously, the method of the invention is effective within 1-2 hours and is non-sedating and non-debilitating.

As used in the specification and claims the term "acetamide" designates N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide and the term "carbonitrile" designates 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

The therapeutically effective amount provided in the treatment of noise phobia may vary according to the specific condition(s) being treated, the size, age and response pattern of the companion animal, the severity of the disorder, the judgment of the attending veterinarian or the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

Companion animals suitable for use in the method of invention include dogs, cats, horses, hamsters, guinea pigs, or any common domesticated pet, preferably dogs.

The compound N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide and a method to prepare said compound is described in US 4,767,765. The compound 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile and a method to prepare said compound is described in US 4,2281,000.

In actual practice, the compounds are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional veterinary pharmaceutical carriers or excipients. Accordingly, the present invention provides a veterinary composition which comprises a veterinary pharmaceutically acceptable carrier and an effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided acetamide or carbonitrile active

ingredient. In tablets, the acetamide or carbonitrile compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Any veterinary pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. The acetamide or carbonitrile compound may be dissolved or suspended in a veterinary pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a veterinary pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable veterinary pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.

Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

For a more clear understanding of the invention, the following examples are set forth herein below. These examples are merely illustrative and are not understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the examples set forth herein below and the foregoing description. Such modifications are also

intended to fall within the scope of the appended claims. Unless otherwise stated, all parts are parts by weight. The term mg/kg designates mg of test compound per kg of body weight of test animal. The term ml/kg designates ml of vehicle or test suspension per kg of body weight of test animal.

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EXAMPLE 1Evaluation of Plasma Concentration Profile of Test Compounds

In this evaluation 8 male Beagle breed dogs, 6 months to 2 years of age, and at least 10 kg in weight were used. Dogs were housed in individual indoor cages in compliance with standards outlined in the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal resources, National Research Council. The dogs were fed an appropriate amount of standard commercial dry ration once per day. Fresh tap water in water bowls was provided *ad libitum*. On the day before the test compounds were administered, food was removed from the dogs by 4:00 pm. Food was withheld until after taking blood samples at the 4 h time point after administration of test materials. Dogs were weighed and ranked by descending weight order and were given physical exams by a veterinarian. The two heaviest dogs were randomly assigned to Group 1 or 2. The second two heaviest dogs were randomly assigned to Group 1 or 2 and so on, until all 8 dogs were placed into either of the two groups. Group 1 with 4 dogs/group, was treated orally with 15 mg/kg of the acetamide test compound and Group 2 was treated orally with 15 mg/kg of the carbonitrile test compound. One week after treatment all dogs were reweighed to ensure correct dosing. Two weeks after treatment, Group 1 was treated orally with 30 mg/kg of the acetamide test compound and Group 2 was treated orally with 30 mg/kg of the carbonitrile test compound. A treatment vial containing an appropriate amount of test compound was provided for each dog. The appropriate amount of vehicle (water containing 0.5% Methocel A4M and 0.01% polysorbate 80) was added to the vial and the contents of the vial were thoroughly mixed. The resultant suspension was withdrawn with an unarmored disposable 12 ml plastic syringe and administered to the dog. Test suspensions were administered to the back of the throat to ensure that they were reliably and completely swallowed by the dog. The vials were rinsed with 0.5 ml vehicle per kg of body weight and the rinsate was administered to the dog. Blood samples were collected at regular time intervals and analyzed for concentration of test compound. The C_{max} value (the maximum compound concentration in the plasma) and the T_{max} value (the time, after dosing, at which the peak compound concentration was obtained) were determined by

200413 13

observation. The calculated mean T_{max} and C_{max} values for each of the four treatments is shown in Table I below. For Table I, the term "Acetamide" designates N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide; and the term "Carbonitrile" designates 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

TABLE I

Treatment	Dose mg/kg	T_{max} hours	C_{max} $\mu\text{g/ml}$
Acetamide	15	0.50	5.59
Acetamide	30	0.88	12.22
Carbonitrile	15	4.25	3.70
Carbonitrile	30	8.25	6.39

EXAMPLE 2

Evaluation of Efficacy of Test Compounds

In this evaluation dogs were screened for noise phobic behaviors and 40 dogs were selected for testing. Male and female Beagles and Mongrels, 1-4.5 years of age and 6.4-18.4 kg body weight were used. Dogs were blocked by weight and by gender and randomly assigned to each of five treatment groups. Dogs were housed in individual indoor cages in a facility in compliance with standards outlined in the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The study was done in four phases, with each phase consisting of five treatment groups of two dogs each. Thus, each of the five treatment groups had eight replicates. Dogs were housed in individual pens and had *ad libitum* access to water. Food was removed from the dogs on the evenings prior to treatment (active and placebo). On the days when dogs were exposed to the noise stimulus, the dogs received food after the observation period ended. During the noise stimulus and observation periods there was minimal contact between the dogs and the observers. All personnel associated with the trial, with the exception of the Study Monitor, were blinded to the five treatments.

Screening:

- Sixteen to twenty-six days prior to testing, a total of 144 dogs were screened for their response to a noise stimulus, which consisted of a 10 minute track of a CD, "Electrifying Thunderstorms". All of the dogs were expected to startle when exposed to the thunderstorm sounds on the CD. Those that exhibited particular behaviors and did not recover quickly from the startle were considered candidates for the study. Behaviors of interest included: panting, pacing, salivating, elimination (urination or defecation), withdrawal, trembling, running around frantically, vocalization, digging and scratching, freezing, and scanning. Efficacy of the test compounds was determined by the post-treatment reduction in the number and/or intensity of these behaviors upon exposure to the noise stimulus.

Definition of Behaviors:

- Panting - breathing quickly or in a labored manner
Pacing - rhythmic, repetitive walking back and forth along the pen
Salivating - excess flow of saliva dripping off the dog's tongue, lips or mouth
Elimination - urination or defecation
Withdrawal - retreating or backing into a corner; dog is alert, non-sleeping
Trembling - shaking involuntarily (with fear)
Running around frantically - fast and nervous, disordered running or circling
Vocalization - barking, crying or whining
Digging and scratching - scraping or digging with the nails
Freezing - to become fixed or motionless
Scanning - back and forth or side to side head movement

Test Procedure:

- For treatment groups A-E in this procedure, the term "Acetamide" designates N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide; and the term "Carbonitrile" designates 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

- Eleven to fifteen days prior to testing, Noise Phobia Screening Forms and videotapes of the dogs were reviewed and 40 dogs were selected for the study. Nine to ten days prior to testing, a veterinarian performed physical exams to ensure the dogs were healthy (e.g. showed no conditions that could produce the non-specific

signs evaluated). Five days prior to testing, 40 dogs were weighed and blocked by weight and gender and randomly allocated to Treatment Groups A-E:

Group A: 15 mg/kg Acetamide

Group B: 5 mg/kg Acetamide

5 Group C: 15 mg/kg Carbonitrile

Group D: 5 mg/kg Carbonitrile

Group E: vehicle (placebo) water containing 0.5% Methocel A4M and 0.01% polysorbate 80

10 Phase 1 consisted of 10 dogs, 2 chosen randomly from each of the 5 treatment groups. For 3 days, ten dogs were acclimated to their environment (video monitored runs). On day 0, the 10 dogs were gavaged with 0.5 ml/kg vehicle. On day 1, the 10 dogs were gavaged with 0.5 ml/kg vehicle. On day 2, the 10 dogs were gavaged with 0.5 ml/kg vehicle and 1 h later were exposed to a 30 minute noise stimulus ("Electrifying Thunderstorms" CD). Dogs were closely monitored via video and observers for 3 h post gavage for the specific behaviors listed above, as well as side effects, including sedation, ataxia, vomiting, disorientation and diarrhea. The amount of time sleeping was also recorded since it was important to distinguish between sleeping (a relaxed state) and anxious behaviors, such as withdrawal. A rating system (0-3) was used for each behavior. Elimination was scored by counting the number of times an animal urinated or defecated during each 5 minute time period. On day 3, the 10 dogs were gavaged with 0.5 ml/kg vehicle. On day 4, the 10 dogs were gavaged with 0.5 ml/kg vehicle. On day 5, the dogs were gavaged with treatments, 2 dogs for each of treatments A-E. The test compounds were suspended in vehicle as described in Example 1. The concentrations of the test compounds were prepared so that the volume given to each animal was 0.5 ml/kg. One h post treatment, the 30 minute noise stimulus was administered. Dogs were closely monitored via video and observers for 3 h post gavage for the specific behaviors listed above, as well as side effects, including sedation, ataxia, vomiting, disorientation and diarrhea. The amount of time sleeping was also recorded since it was important to distinguish between sleeping (a relaxed state) and anxious behaviors, such as withdrawal. A rating system (0-3) was used for each behavior. Elimination was scored by counting the number of times and animal urinated or defecated during each 5 minute time period. All observers were blinded with regard

to treatments. Phase 2, Phase 3 and Phase 4, each consisting of 10 dogs not used in a previous phase, 2 from each of the 5 treatment groups, were run on subsequent weeks.

Results and Discussion:

5 Behaviors were analyzed by the one-sided Fisher's Exact test and by ANOVA procedures, comparing the differences in pretreated versus treated scores for each animal, as well as comparing the scores of all treatment groups to each other (only "after treatment"). Based on these analyses, there were significant treatment effects observed, particularly at the 15 mg/kg doses of each test compound. Behaviors
10 demonstrating statistical significance included panting, trembling, withdrawal, scanning and vocalization. It is particularly noteworthy that dogs treated with 15 mg/kg of test compound had significantly lower trembling scores, which the CD played, compared with the untreated control animals. Sedation, ataxia and disorientation were not observed for any of the treated dogs.

15

What is claimed is:

1. A method for the treatment and prevention of noise phobia in a companion animal which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.
2. The method according to claim 1 wherein the companion animal is selected from the group consisting essentially of a dog; cat; horse; hamster; and guinea pig.
3. The method according to claim 1 wherein the companion animal is a dog.
4. The method according to claim 3 which comprises providing said animal with a therapeutically effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide.
5. The method according to claim 1 wherein said effective amount is about 0.5 mg/kg-50 mg/kg.
6. The method according to claim 3 wherein said effective amount is about 5.0mg/kg-40 mg/kg.
7. The method according to claim 3 wherein said acetamide or carbonitrile is provided orally.
8. A veterinary composition which comprises a veterinary pharmaceutically acceptable carrier and an effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

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9. The composition according to claim 8 which comprises an effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide.

5 10. The composition according to claim 8 wherein said veterinary pharmaceutically acceptable carrier is a liquid carrier.

11. The composition according to claim 8 wherein said veterinary pharmaceutically acceptable carrier is a solid carrier.

10

12. The composition according to claim 8 wherein the effective amount is sufficient to provide about 0.5 mg/kg-50 mg/kg of active ingredient.

13. The composition according to claim 9 wherein the effective amount is
15 sufficient to provide about 5.0mg/kg-40 mg/kg of active ingredient

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MÉTODO PARA EL TRATAMIENTO DE FOBIA AL RUIDO EN ANIMALES DE
COMPañÍA

ANTECEDENTES DE LA INVENCION

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Esta solicitud reivindica el beneficio bajo el 35 U.S.C. § 119(e) a la solicitud provisional co-pendiente U.S. no. 60/684669, presentada en mayo 26, 2005, que se incorpora aquí como referencia en su totalidad.

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Las fobias al ruido y a las tormentas con truenos están entre las afecciones más comúnmente reconocidas asociadas con el pánico o respuestas fóbicas en animales de compañía tales como perros, gatos o caballos, particularmente perros. Las tormentas con truenos, los fuegos artificiales, el fuego de las armas, los petardeos de los carros, etc., inducen frecuentemente síntomas clínicos no específicos indeseables en animales de compañía, particularmente perros, tales como salivación, defecación, orina, destrucción, escape, temblor con ocultamiento, vocalización y similares. Los tratamientos conocidos para el comportamiento de ansiedad general en animales de compañía involucran generalmente ataques a largo plazo, es decir 3-4 semanas, o si actúan rápido, causan sedación y/o ataxia. Sin embargo, la mayoría de los propietarios de los animales de compañía y los veterinarios preferirían tratar los animales que sufren de fobia al ruido con un método que no promueva la sedación o ataxia y que sea efectiva a la hora o dos horas de administración.

Por lo tanto, es un objeto de esta invención suministrar un método terapéuticamente efectivo para el tratamiento de fobia al ruido en un animal de compañía que no sea sedante.

5

También es un objeto de la invención suministrar una composición veterinaria que sea útil para el tratamiento de fobia al ruido en un animal de compañía.

10

Ésta es una característica de la invención en donde el método para el tratamiento efectivo de la fobia al ruido en un animal de compañía, particularmente un perro, es de acción rápida y no origina ataxia.

15

Otros objetos y características de la invención serán más evidentes de la descripción detallada establecida aquí adelante.

RESUMEN DE LA INVENCION

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La presente invención suministra un método para el tratamiento y prevención de fobia al ruido en un animal de compañía que comprende suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-
25 1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

También se suministra una composición veterinaria para el tratamiento efectivo de fobia al ruido en un animal de compañía.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

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Los propietarios de los animales de compañía y los veterinarios se esfuerzan por encontrar los medios para controlar la fobia al ruido en sus animales tales como perros, gatos y caballos, particularmente perros. Los comportamientos de la fobia al ruido pueden incluir ocultamiento, exploración, orina, defecación, resuello, masticamiento, marcha, escape, temblor, vocalización y similares. Las terapias conocidas utilizadas para la fobia al ruido incluyen terapias de uso extraoficial tales como clomipramina, amitriptilina y buspirona que pueden tomar más de 3-4 semanas antes de que su efecto sea evidente, o el uso de benzodiacepinas, acepromacina o antidepresivos que actúan más rápidamente pero a menudo causan sedación y ataxia.

25

Sorprendentemente, se ha encontrado ahora que el N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida (acetamida) o el 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo (carbonitrilo) es útil para el tratamiento terapéutico y la prevención de la fobia al ruido en un animal de compañía sin causar sedación o ataxia y con un período acortado de ataque. De acuerdo con esto la presente invención suministra un

método para el tratamiento y prevención de la fobia al ruido en un animal de compañía que comprende a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

Ventajosamente, el método de la invención es efectivo a las 1-2 horas y no es sedante y no es debilitante.

Como se utiliza en esta especificación y reivindicaciones el término "acetamida" designa N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida y el término "carbonitrilo" designa el 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

El término "suministrar" como se utiliza aquí con respecto a suministrar un compuesto o una sustancia abarcada por la invención, designa administrar directamente tal compuesto o sustancia, o administrar una prodroga, derivado o análogo que forma una cantidad equivalente del compuesto o sustancia en el cuerpo.

La cantidad terapéuticamente efectiva suministrada en el tratamiento de la fobia al ruido puede variar de acuerdo con la condición específica a ser tratada, el tamaño, la edad y el patrón de respuesta del animal de compañía, la severidad de la afección, el juicio del veterinario que atiende o similares. En general, las cantidades efectivas para la administración oral diaria pueden ser de aproximadamente 0.01

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a 1,000 mg/kg, preferiblemente aproximadamente 0.5 a 500 mg/kg y cantidades efectivas para la administración parenteral pueden ser aproximadamente 0.1 a 100 mg/kg, preferiblemente aproximadamente 0.5 a 50 mg/kg.

5

Los animales de compañía adecuados para uso en el método de la invención incluyen perros, gatos, caballos, hámsteres, conejillos de indias, o cualquier animal doméstico común, preferiblemente los perros.

10

El compuesto N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-yl)fenil]acetamida y un método para preparar dicho compuesto se describe en la US 4,767,765. El compuesto 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo y un
15 método para preparar dicho compuesto se describen en la US 4,2281,000.

En la práctica actual, los compuestos se suministran al administrar el compuesto o un precursor de éste en una forma
20 sólida o líquida, sea pura o en combinación con uno o más portadores o excipientes farmacéuticos veterinarios convencionales. De acuerdo con esto, la presente invención suministra una composición veterinaria que comprende un
25 portador veterinario farmacéuticamente aceptable y una cantidad efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

Los portadores sólidos adecuados para el uso en la composición de la invención incluyen una o más sustancias que también pueden actuar como agentes saborizantes, lubricantes, solubilizantes, agentes de suspensión, llenadores, deslizantes, ayudas de compresión, ligadores, agentes desintegrantes de tableta o materiales encapsulantes. En los polvos, el portador puede ser un sólido finamente dividido que está en mezcla con un ingrediente activo acetamida o carbonitrilo finamente dividido. En las tabletas, el compuesto de acetamida o carbonitrilo se puede mezclar con un portador que tiene las propiedades de compresión necesarias en las proporciones adecuadas y compactado en la forma y tamaño deseados. Dichos polvos y tabletas pueden contener hasta el 99% en peso del compuesto de fórmula I. Los portadores sólidos adecuados para el uso en la composición de la invención incluyen fosfato de calcio, estearato de magnesio, talco, azúcares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, carboximetilcelulosa de sodio, polivinilpirrolidina, ceras con bajo punto de fusión y resinas intercambiadoras de ión.

Cualquier portador líquido veterinario farmacéuticamente aceptable adecuado para preparar soluciones, suspensiones, emulsiones, jarabes y elixires se puede emplear en la composición de la invención. El compuesto de acetamida o carbonitrilo se puede disolver o suspender en un portador líquido veterinario farmacéuticamente aceptable tal como agua, un disolvente orgánico, o un aceite o grasa veterinaria

farmacéuticamente aceptable, o una mezcla de éste. Dicha composición líquida puede contener otros aditivos farmacéuticos veterinarios adecuados tales como solubilizadores, emulsificadores, amortiguadores, preservativos, endulzantes, agentes saborizantes, agentes de suspensión, agentes espesantes, agentes colorantes, reguladores de la viscosidad, estabilizadores, osmoreguladores, o similares. Ejemplos de portadores líquidos adecuados para la administración oral y parenteral incluyen agua (particularmente lo que contiene aditivos tales como los anteriores, por ejemplo, derivados de celulosa, preferiblemente solución de carboximetilcelulosa de sodio), alcoholes, (incluyendo alcoholes monohídricos y alcoholes polihídricos, por ejemplo, glicoles) o sus derivados, o aceites (por ejemplo, aceite de coco fraccionado y aceite de araquís). Para la administración parenteral el portador también puede ser un éster aceitoso tal como etil oleato o isopropil miristato.

Las composiciones de la invención que son soluciones o suspensiones estériles son adecuadas para inyección intramuscular, intraperitoneal o subcutánea. Las soluciones estériles también se pueden administrar intravenosamente. Las composiciones de la invención adecuadas para la administración oral pueden estar en forma de composición líquida o sólida.

Para un entendimiento más claro de la invención, se establecen los siguientes ejemplos aquí adelante. Estos ejemplos son simplemente ilustrativos y no se entienden en el sentido de limitar el alcance y los principios subyacentes de la invención de ninguna manera. De hecho, varias modificaciones de la invención, además de aquellas mostradas y descritas aquí, serán evidentes para aquellos expertos en la técnica de los ejemplos establecidos aquí adelante y de la descripción siguiente. Tales modificaciones también pretender estar dentro del alcance de las reivindicaciones anexas. A menos que se establezca otra cosa, todas las partes son partes en peso. El término mg/kg designa mg del compuesto de prueba por kg del peso corporal del animal de prueba. El término ml/kg designa ml del vehículo o suspensión de prueba por kg de peso corporal del animal de prueba.

EJEMPLO 1

Evaluación del Perfil de Concentración de Plasma de los

Compuestos de Prueba

En esta evaluación se utilizaron 8 perros de raza Beagle machos, de 6 meses a 2 años de edad, y por lo menos 10 kg de peso. Los perros fueron puestos en jaulas individuales a resguardo en cumplimiento con los estándares prescritos en la Guía para el Cuidado y Uso de Animales de Laboratorio del Instituto de Recursos de Animales de Laboratorio, Consejo de Investigación Nacional. Los perros se alimentaron con una

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cantidad apropiada de ración seca comercial estándar una vez por día. Agua fresca de llave en tazones para agua se suministró *ad libitum*. El día antes de que los compuestos de prueba se administraran, se le retiró el alimento a los

5 perros hacia las 4:00 pm. El alimento fue mantenido hasta después de tomar las muestras de sangre en el punto de tiempo de las 4 h después de la administración de los materiales de prueba. Los perros se pesaron y escalonados en orden de peso descendente y se les realizaron exámenes físicos por un

10 veterinario. Los dos perros más pesados fueron asignados aleatoreamente al Grupo 1 o 2. Los segundos dos perros más pesados fueron asignados aleatoriamente al Grupo 1 o 2 y así sucesivamente, hasta que los 8 perros se colocaron en cualquiera de los dos grupos. El Grupo 1 con 4 perros/grupo,

15 se trató oralmente con 15 mg/kg del compuesto de prueba de acetamida y el Grupo 2 se trató oralmente con 15 mg/kg del compuesto de prueba carbonitrilo. Una semana después del tratamiento todos los perros se pesaron de nuevo para asegurar la correcta dosificación. Dos semanas después del

20 tratamiento, el Grupo 1 se trató oralmente con 30 mg/kg del compuesto de prueba de acetamida y el Grupo 2 se trató oralmente con 30 mg/kg del compuesto de prueba carbonitrilo. Un recipiente de tratamiento* que contiene una cantidad apropiada del compuesto de prueba se suministró a cada perro.

25 La cantidad apropiada del vehículo (agua que contiene 0.5% de Metocel A4M y 0.01% de polisorbato 80) se agregó al frasco y los contenidos del frasco fueron completamente mezclados. La suspensión resultante se retiró con una jeringa plástica

desechable de 12 ml desarmada y administrada al perro. Las suspensiones de prueba se administraron a la parte trasera de la garganta para asegurar que ellas fueran confiables y completamente tragadas por el perro. Los frascos se enjuagaron con 0.5 ml de vehículo por kg de peso corporal y el enjuague se administró al perro. Se recolectaron muestras de sangre a intervalos de tiempo regulares y se analizaron para la concentración del compuesto de prueba. El valor C_{max} (concentración de compuesto máxima en el plasma) y el valor T_{max} (el tiempo, después de dosificación, en el cual se obtuvo la concentración del compuesto pico) se determinaron mediante observación. Los valores medios calculados T_{max} y C_{max} para cada uno de los cuatro tratamientos se muestran en la Tabla I de adelante. Para la Tabla I el término "Acetamida" designa N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida; y el término "Carbonitrilo" designa 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

TABLA I

Tratamiento	Dosis mg/kg	T_{max} horas	C_{max} µg/ml
Acetamida	15	0.50	5.59
Acetamida	30	0.88	12.22
Carbonitrilo	15	4.25	3.70
Carbonitrilo	30	8.25	6.39

EJEMPLO 2Evaluación de la Eficacia de los Compuestos de Prueba

5 En esta evaluación los perros se seleccionaron por los
comportamientos fóbicos al ruido y se seleccionaron 40 perros
para la prueba. Se utilizaron Beagles y Nongrels machos y
hembras, de 1-4.5 años de edad y 6.4-18.4 kg de peso
corporal. Los perros puestos en bloques de acuerdo con el
10 peso y el género y asignados aleatoriamente a cada uno de los
cinco grupos de tratamiento. Los perros fueron puestos en
jaulas individuales a resguardo en una instalación en
cumplimiento con los estándares prescritos en la Guía para el
Cuidado y Uso de Animales de Laboratorio del Instituto de
15 recursos de Animales de Laboratorio, Consejo de Investigación
Nacional. El estudio se hizo en cuatro fases, consistiendo
cada una de las fases de cinco grupos de tratamiento de dos
perros cada uno. Así, cada uno de los cinco grupos de
tratamiento tuvo ocho replicas. Los perros fueron puestos en
20 corrales individuales y tuvieron acceso al agua *ad libitum*.
La comida se retiró de los perros en las noches antes del
tratamiento (activo y placebo). En los días cuando los perros
fueron expuestos al estímulo de ruido, los perros recibieron
agua después de la finalización del período de observación.
25 Durante el estímulo de ruido y los períodos de observación
hubo contacto mínimo entre los perros y los observadores.
Todo el personal asociado con el ensayo, con la excepción del

Monitor del Estudio, estuvieron ciegos a los cinco tratamientos.

Selección:

Dieciséis a veintiséis días antes de la prueba, se seleccionaron un total de 144 perros por su respuesta a estímulos de ruido, que consistía de un seguimiento de 10 minutos de un CD, "Tormentas Eléctricas con Truenos". Se esperaba que todos los perros se espantaran cuando se expusieran a los sonidos de los truenos de tormenta en el CD. Aquellos que exhibieron comportamientos particulares y no se recuperaron rápidamente del espanto se consideraron candidatos para el estudio. Los comportamientos de interés incluían: jadeo, marcha, salivación, eliminación (orina o defecación), retirada, temblor, correr frenéticamente en los alrededores, vocalización, cavamiento, y rasguñado, congelamiento, y exploración. La eficacia de los compuestos de prueba se determinó mediante reducción post-tratamiento en el número y/o intensidad de estos comportamientos luego de la exposición al estímulo de ruido.

Definición de los Comportamientos:

Ladeamiento - respiración rápida o de una manera trabajosa.

Marcha - caminado hacia atrás rítmico, repetitivo y hacia delante a lo largo de la jaula.

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Salivación - exceso de flujo de saliva que gotea de la lengua del perro, labios o boca.

Eliminación - orina o defecación.

Retiro - retirarse o irse hacia atrás a una esquina; el perro
5 está alerta, no duerme.

Temblor - agitación involuntaria (con temor)

Correr frenéticamente alrededor - correr o hacer círculos de manera rápida y nerviosa, desordenada.

Vocalización - ladrar, llorar o gemir.

10 Cavar y rastrillar - rastrillar o cavar con las uñas.

Congelamiento - quedar fijo o sin movimiento.

Explorar - movimiento de la cabeza de atrás hacia delante o de lado a lado.

15 **Procedimiento de Prueba:**

Para los grupos de tratamiento A-E en este procedimiento, el término "Acetamida" designa N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-
20 il)fenil]acetamida; y el término "Carbonitrilo" designa 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

Once a quince días antes de la prueba, las Formas de Selección de Fobia al Ruido y video cintas de los perros se
25 revisaron y se seleccionaron 40 perros para el estudio. Nueve a diez días antes de la prueba, un veterinario desarrolló exámenes físicos para asegurarse que los perros estuvieran saludables (por ejemplo, que no mostraran condiciones que

pudieran producir signos evaluados no específicos). Cinco días antes de la prueba, 40 perros se pesaron y se pusieron en bloques por peso y género y se situaron aleatoriamente en los Grupos de Tratamiento A-E:

Grupo A: 15 mg/kg de Acetamida

Grupo B: 5 mg/kg de Acetamida

Grupo C: 15 mg/kg de Carbonitrilo

Grupo D: 5 mg/kg de Carbonitrilo

Grupo E: vehículo (placebo) agua que contiene 0.5% de Metocel A4M y 0.01% de polisorbato 80

La fase 1 consistió de 10 perros, 2 escogidos aleatoriamente de cada uno de los 5 grupos de tratamiento.

Durante 3 días, diez perros fueron aclimatados a su ambiente (corridas monitoreadas por video). En el día 0, los 10 perros fueron cebados con 0.5 ml/kg de vehículo. En el día 1, los 10 perros fueron cebados con 0.5 ml/kg de vehículo. En el día 2, los 10 perros fueron cebados con 0.5 ml/kg de vehículo y 1 h más tarde fueron expuestos a estímulos de 30 minutos de ruido (CD con "Tormentas Eléctricas con Truenos"). Los perros fueron cercanamente monitoreados por vía de video y los observadores durante 3 h luego del cebado para los comportamientos específicos listados anteriormente, así como también los efectos colaterales, incluyendo sedación, ataxia, vómito, desorientación y diarrea. La cantidad de tiempo de sueño también se registró en razón a que era importante distinguir entre sueño (un estado relajado) y comportamientos

ansiosos, tales como el de retiro. Un sistema de calificación (0-3) se utilizó para cada comportamiento. La eliminación se calificó al contar el número de veces que el animal orinó o defecó durante cada período de tiempo de 5 minutos. En el día 3, los 10 perros fueron cebados con 0.5 ml/kg de vehículo. En el día 4, los 10 perros fueron cebados con 0.5 ml/kg de vehículo. En el día 5, los perros fueron cebados con tratamientos, 2 perros para cada uno de los tratamientos A-E. Los compuestos de prueba se suspendieron en el vehículo como se describió en el Ejemplo 1. Las concentraciones de los compuestos de prueba se prepararon de tal forma que el volumen dado a cada animal fue de 0.5 ml/kg. Una h post tratamiento, se administró el estímulo de 30 minutos de ruido. Los perros se monitorearon cercanamente por vía de video y los observadores durante 3 h post cebado por los comportamientos específicos listados anteriormente, así como también los efectos colaterales, que incluyen sedación, ataxia, vómito, desorientación y diarrea. La cantidad de tiempo de sueño también se registró en razón a que era importante distinguir entre sueño (un estado relajado) y comportamientos ansiosos, tales como retiro. Un sistema de calificación (0-3) se utilizó para cada comportamiento. La eliminación se calificó al contar el número de veces que el animal orinó o defecó durante cada período de tiempo de 5 minutos. Todos los observadores estuvieron ciegos con relación a los tratamientos. La Fase 2, Fase 3 y la Fase 4, consistió cada una de 10 perros no utilizados en una fase

previa, 2 de cada uno de los 5 grupos de tratamiento, corrieron en semanas posteriores.

Resultados y Discusión:

5 Los comportamientos se analizaron mediante la prueba Exacta de Fisher de un lado y los procedimientos ANOVA, comparando las diferencias en el pretratado versus las calificaciones tratadas para cada animal, así como también
10 comparar las calificaciones para todos los grupos de tratamiento uno con el otro (solamente "después de tratamiento"). Con base en estos análisis, hubo efectos de tratamiento observados, particularmente en las dosis de 15 mg/kg de los compuestos de prueba. Los comportamientos
15 demuestran significancia estadística incluidos jadeo, temblor, retiro, exploración y vocalización. Es particularmente notorio que los perros tratados con 15 mg/kg del compuesto de prueba tuvieron unas calificaciones de temblor significativamente inferiores, cuando sonó el CD,
20 comparado con los animales de control no tratados. La sedación, ataxia y la desorientación no se observó para ninguno de los perros tratados.

REIVINDICACIONES

1. Un método para el tratamiento y prevención de fobia al ruido en un animal de compañía que comprende suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.
2. El método de acuerdo a la reivindicación 1 en donde el animal de compañía se selecciona del grupo que consiste esencialmente de un perro; gato; caballo; hámster; y conejillo de indias.
3. El método de acuerdo a la reivindicación 1 en donde el animal de compañía es un perro.
4. El método de acuerdo a la reivindicación 3 que comprende suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida.
5. El método de acuerdo a la reivindicación 1 en donde dicha cantidad efectiva es de aproximadamente 0.5 mg/kg-50 mg/kg.

6. El método de acuerdo a la reivindicación 3 en donde dicha cantidad efectiva es de aproximadamente 5.0 mg/kg-40 mg/kg.

5 7. El método de acuerdo a la reivindicación 3 en donde dicha acetamida o carbonitrilo se suministra oralmente.

10 8. Una composición veterinaria que comprende un portador veterinario farmacéuticamente aceptable y una cantidad efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

15 9. La composición de acuerdo a la reivindicación 8 que comprende una cantidad efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida.

20 10. La composición de acuerdo a la reivindicación 8 en donde dicho portador veterinario farmacéuticamente aceptable es un portador líquido.

25 11. La composición de acuerdo a la reivindicación 8 en donde dicho portador veterinario farmacéuticamente aceptable es un portador sólido.

12. La composición de acuerdo a la reivindicación 8 en donde la cantidad efectiva es suficiente para suministrar aproximadamente 0.5 mg/kg-50 mg/kg del ingrediente activo.

5

13. La composición de acuerdo a la reivindicación 9 en donde la cantidad efectiva es suficiente para suministrar aproximadamente 5.0 mg/kg-40 mg/kg del ingrediente activo.

MÉTODO PARA EL TRATAMIENTO DE FOBIA AL RUIDO EN ANIMALES DECOMPañÍA

5

RESUMEN DE LA INVENCION

La presente invención suministra un método para el tratamiento no sedante de fobia al ruido en un animal de compañía, particularmente un perro, que comprende
10 suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

PATENT COOPERATION TREATY

PCT/US2006/019685

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

LENCES, Barbara, L.
Wyeth
Patent Law Department
Five Giralda Farms
Madison, New Jersey 07940
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 18 August 2006 (18.08.2006)	
Applicant's or agent's file reference AM102099	IMPORTANT NOTIFICATION
International application No. PCT/US2006/019685	International filing date (day/month/year) 22 May 2006 (22.05.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 26 May 2005 (26.05.2005)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides 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 a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides 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 a time limit which is reasonable under the circumstances.

Priority datePriority application No.Country or regional Office
or PCT receiving OfficeDate of receipt
of priority document

26 May 2005 (26.05.2005)

60/684,669

US

21 July 2006 (21.07.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Beate Giffo-Schmitt

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Telephone No. +41 22 338 92 41

PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

NOV 17 2006

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

WYETH

Attn: Lences, Barbara L.

Patent Law Department

Five Giralda Farms

Madison, New Jersey 07940

ETATS-UNIS D'AMERIQUE

(PCT Rule 44.1)

Date of mailing
(day/month/year)

08/11/2006

Applicant's or agent's file reference

AM102099

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2006/019685

International filing date
(day/month/year)

22/05/2006

Applicant

WYETH

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are 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 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

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 and the written opinion of the International Searching Authority are 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. Reminders

Shortly after the expiration of 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.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, 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); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

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.

Name and mailing address of the International Searching Authority



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

Authorized officer

Dominique Hundt

RECEIVED

NOV 17 2006

SHIELD

CC: PRINCETON

000-1 41

NOTES TO FORM PCT/ISA/220

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 and the written opinion of the International Searching Authority, 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 latter 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 (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

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 16 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/is 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 (Section 205(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.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM102099	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/019685	International filing date (day/month/year) 22/05/2006	(Earliest) Priority Date (day/month/year) 26/05/2005
Applicant WYETH		

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 5 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
☐ a translation of the International application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (see Box No. III)

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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

0002343

International application No
PCT/US2006/019685

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5025 A61K31/519 A61P25/00

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)

A61K A61P

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, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 767 765 A (ALBRIGHT ET AL) 30 August 1988 (1988-08-30) cited in the application claims	1-13
X	US 5 169 850 A (DUSZA ET AL) 8 December 1992 (1992-12-08) column 1, lines 1-24; claims column 9, lines 40-52 column 7, lines 43-52 column 12, lines 33-37 - lines 44-48 column 12, lines 54-58	1-13
	-/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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
- *Z* document member of the same patent family

Date of the actual completion of the International search

30 October 2006

Date of mailing of the international search report

08/11/2006

Name and mailing address of the ISA/

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

Authorized officer

Blott, Catherine

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/019685

C(Continuation), DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 281 000 A (DUSZA ET AL) 28 July 1981 (1981-07-28) cited in the application column 4, lines 45-55; claims column 5, line 4 column 7, lines 14-16	1-13
A	SHULL-SELCER E A ET AL: "ADVANCES IN THE UNDERSTANDING AND TREATMENT OF NOISE PHOBIAS" VETERINARY CLINICS OF NORTH AMERICA SMALL ANIMAL PRACTICE, vol. 21, no. 2, 1991, pages 353-368, XP009072672 ISSN: 0195-5616 page 364 - page 365	1-13
A	CROWELL DAVIS S L LO - KANSAS CITY, MO., USA: "Psychopharmacology Part II: anxiolytics, hormones, narcotic antagonists and miscellaneous." PROC.CENT.VET.CONF (1999 MEET., 108-11) 6 REF. AV - NO REPRINT ADDRESS., 1999, XP009073323 page 108	1-13

00045 45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/019685

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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 1-7 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:
- 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 III Observations where unity of invention is lacking (Continuation of item 3 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.

00006 46

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/019685

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4767765	A	30-08-1988	NONE	
US 5169850	A	08-12-1992	NONE	
US 4281000	A	28-07-1981	AR 227766 A1	15-12-1982
			AU 536081 B2	19-04-1984
			AU 5951780 A	15-01-1981
			CA 1140125 A1	25-01-1983
			DD 153840 A5	03-02-1982
			DE 3065270 D1	17-11-1983
			EP 0025819 A1	01-04-1981
			GR 70075 A1	27-07-1982
			HU 182153 B	28-12-1983
			IL 60330 A	31-05-1984
			PL 225541 A1	30-10-1981
			YU 172280 A1	28-02-1983

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2006/019685

International filing date (day/month/year)
22.05.2006

Priority date (day/month/year)
26.05.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/5025 A61K31/519 A61P25/00

Applicant
WYETH

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

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

2. FURTHER ACTION

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

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

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

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Blott, Catherine

Telephone No. +49 89 2399-7538



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/019685

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/019685

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

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

- ☐ the entire international application
- ☒ claims Nos. 1-7 (industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 1-7 (industrial applicability) relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13~~ter~~.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/019685

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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

1. Statement

Novelty (N)	Yes: Claims	1-7
	No: Claims	
Inventive step (IS)	Yes: Claims	1-13
	No: Claims	
Industrial applicability (IA)	Yes: Claims	8-13
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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Re Item III

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

1. Claims 1-7 relate to a subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

2. This Authority considers that there are 2 inventions covered by the claims indicated as follows:
 - I: Claims 1-13 directed to veterinary compositions comprising N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide (compound A) and their use for the treatment and prevention of noise phobia in a companion animal
 - II: Claims 1-3, 5-8 directed to veterinary compositions comprising 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (compound B) and their use for the treatment and prevention of noise phobia in a companion animal

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by the present invention is to provide a medicament for treating noise phobia in companion animals.

The proposed solution is to use a therapeutically effective amount of a compound selected from:

- 1) N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide (compound A) and
- 2) 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (compound B)

The treatment of noise phobia represents the technical feature, which, a priori, unify the different compounds A) and B).

The treatment of noise phobia in animals has already been addressed in several documents of the prior art (cf. e.g. D6-8). Anxiolytics are one group of drugs utilised

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to treat noise phobia.

Consequently, the treatment of noise phobia can no longer serve as a single general inventive concept linking the different compounds A) and B), which have no other special technical features in common, their structures being markedly different.

Therefore, the use of compounds A) and B) in the treatment of noise phobia represent each a distinct invention, characterized by its own special technical feature, i.e. the structural feature of the compound.

In the present application, no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual compounds.

The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Nevertheless, the search was carried out for all inventions and the present opinion was based on all of them.

Re Item V

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

3. Reference is made to the following documents:

- D1: US-A-4 767 765 (ALBRIGHT ET AL) 30 August 1988 (1988-08-30) cited in the application
- D2: US-A-5 169 850 (DUSZA ET AL) 8 December 1992 (1992-12-08)
- D3: US-A-4 281 000 (DUSZA ET AL) 28 July 1981 (1981-07-28) cited in the application
- D4: SHULL-SELCER E A ET AL: "ADVANCES IN THE UNDERSTANDING AND TREATMENT OF NOISE PHOBIAS" VETERINARY CLINICS OF NORTH AMERICA SMALL ANIMAL PRACTICE, vol. 21, no. 2, 1991, pages 353-368,

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International application No.

PCT/US2006/019685

XP009072672 ISSN: 0195-5616

D5: CROWELL DAVIS S L LO - KANSAS CITY, MO., USA: "Psychopharmacology Part II: anxiolytics, hormones, narcotic antagonists and miscellaneous." PROC.CENT.VET.CONF (1999 MEET., 108-11) 6 REF. AV - NO REPRINT ADDRESS., 1999, XP009073323

D1: Treatment of anxiety or inducing sedation or hypnosis in mammals - by admin. of 6-(3-acylamino-phenyl)-1,2,4-triazolo-(4,3-B)pyridazine derivs. such as e.g. N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide (compound A). Tests were done in animals. The compounds are administered in amounts ranging from about 0.1 mg to about 20.0 mg/kg of body weight per day.

D2: Pyrazolo(1,5-a)pyrimidine-3-carboxamide derivs. such as e.g. 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (compound B) are neurotropic and anxiolytic agents - useful for the treatment of cognitive deterioration, anxiety and hypertension in mammals and more particularly in animals.

D3: 7-Heterocyclyl-pyrazolo-(1,5-A)-pyrimidine derivs. such as e.g. 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (compound B) - useful as CNS active agents esp. anxiolytics in mammals. The compounds are administered in amounts ranging from about 0.1 mg to about 20.0 mg/kg of body weight per day. Tests were done in animals.

D4-5: Use of anxiolytics for the treatment of noise phobias in companion animals.

4. a) The present application does not meet the criteria of Art. 33(1) PCT, because the subject-matter of claim 8, i.e. a veterinary composition which comprises a veterinary pharmaceutically acceptable carrier and an effective amount of N-methyl-N-[3-(3-methyl-1,2,4-triazolo-[4,3-b]pyridazin-6-yl)phenyl]acetamide (compound A) or 7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (compound B), is not new in the sense of Art. 33(2) PCT.

The document D1 already discloses pharmaceutical compositions for mammals comprising compound A.

The documents D2-3 already disclose pharmaceutical compositions for mammals comprising compound B.

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b) Dependent claims 9-13 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1-5 and the corresponding passages cited in the search report.

5. a) The present application does not meet the criteria of Art. 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Art. 33(3) PCT.

The documents D4-5 are regarded as being the closest prior art to the subject-matter of claim 1, and disclose the use of anxiolytics for the treatment of noise phobias.

The subject-matter of claim 1 therefore differs from D4-5 in that compound A or B are used to treat the noise phobia.

In the tests of the present application, it was shown that behaviors such as panting, trembling, withdrawal, scanning and vocalization were significantly ameliorated. The dogs treated with compound A or B had slower trembling score. Sedation, ataxia and disorientation were not observed.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative treatment for the therapy of noise phobia.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Art. 33(3) PCT) for the following reasons.

It is already known from D1-3, that compounds A and B are useful anxiolytics for the treatment of anxiety in mammals.

Testing further anxiolytic agents such as compound A or B thus would be a matter of routine for the man skilled in the art aiming to find a new medicament for the treatment of noise phobia,

This is all the more true as e.g. D2-3 do not reveal any sedative or other disadvantageous effects of the drug B.

The subject-matter of claim 1 thus is rendered obvious by the teaching of D1-3 in combination with D4-5 and does not involve an inventive step (Art. 33(3) PCT).

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- b) Dependent claims 2-7 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1-5 and the corresponding passages cited in the search report.
6. For the assessment of the present claims 1-7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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000076

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
(21) N° de solicitud:		(51) Int Cl: A61K 31/5025, A61K 31/519, A61P 25/00	
22) Fecha de solicitud:		(71) Solicitante(s) WYETH	
(30) Prioridad	(31) No. 60/684,669	32) Fecha 26/05/05	(33) País US
		(72) Inventor(es) ENOS, AnnMarie; EPPLER, Cecil Mark y POWELL, Dennis William	
		(74) Apoderado: ALVARO CORREA ORDOÑEZ	
(85) Fecha límite inicio fase nacional: 26/12/07		(87) Publicación internacional	
(86) Datos relativos a la presentación de la solicitud PCT		Fecha: 30/11/06	
Fecha de presentación de la solicitud: 22/05/06		N° publicación: WO/2006/127574	
No. de solicitud PCT/US2006/019685			
(54) Título: MÉTODO PARA EL TRATAMIENTO DE FOBIA AL RUIDO EN ANIMALES DE COMPAÑÍA			

Reivindicación(es):

1. Un método para el tratamiento y prevención de fobia al ruido en un animal de compañía que comprende suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-[4,3-b]piridazin-6-il)fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.

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 Industria y Comercio		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO		00057
		DIVISION DE NUEVAS CREACIONES		
SUPERINTENDENCIA PATENTE DE INVENCION ☐ PCT ☒ MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐				
(21) N° de solicitud:		(22) Fecha de solicitud:		
(51) Clasificación Internacional: A61K 31/5025, A61K 31/519, A61P 25/00				
(71) Solicitante(s) WYETH				
(72) Inventor(es) ENOS, AnnMarie; EPPLER, Cecil Mark y POWELL, Dennis William				
(74) Apoderado: ALVARO CORREA ORDOÑEZ				
(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) País	
	60/684,669	26/05/05	US	
(85) Fecha inicio fase nacional: 26/12/07		(87) Publicación internacional		
(86) Datos relativos a la presentación de la solicitud PCT		Fecha: 30/11/06		
Fecha de presentación de la solicitud: 22/05/06		N° publicación: WO/2006/127574		
No. de solicitud PCT/US2006/019685				
(54) Título:				
METODO PARA EL TRATAMIENTO DE FOBIA AL RUIDO EN ANIMALES DE COMPAÑIA				

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 Industria y Comercio		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES		<u>00058</u>
		TARJETA ARCHIVO TEMATICO SUPERINTENDENCIA PATENTE DE INVENCIÓN PCT ☒ MODELO DE UTILIDAD DISEÑO INDUSTRIAL		
(1) N° de solicitud:		(22) Fecha de solicitud:		
(31) Clasificación Internacional : A61K 31/5025, A61K 31/519, A61P 25/00				
(71) Solicitante(s) WYETH				
(72) Inventor(es) ENOS, AnnMarie; EPPLER, Cecil Mark y POWELL, Dennis William				
(74) Apoderado: ALVARO CORREA ORDOÑEZ				
(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) País	
	60/684,669	26/05/05	US	
(85) Fecha límite inicio fase nacional: 26/12/07		(87) Publicación internacional:		
(86) Datos relativos a la presentación de la solíc. PCT		Fecha: 30/11/06		
Fecha de presentación de la solicitud: 22/05/06		No. Publicación : WO/2006/127574		
No. de solicitud PCT/US2006/019685				
(54) Título:				
MÉTODO PARA EL TRATAMIENTO DE FOBIA AL RUIDO EN ANIMALES DE COMPAÑÍA				
(57) Resumen: La presente invención suministra un método para el tratamiento no sedante de fobia al ruido en un animal de compañía, particularmente un perro, que comprende suministrarle a dicho animal una cantidad terapéuticamente efectiva de N-metil-N-[3-(3-metil-1,2,4-triazolo-3-b)piridazin-6-il]fenil]acetamida o 7-(3-piridil)pirazolo[1,5-a]pirimidina-3-carbonitrilo.				

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-123649- -00000-0000

Fecha: 2007-11-22 18:11:41 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 58



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

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 presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA []

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 y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se 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 trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Claudia M. Novo Cortes
Firma Responsable

Fecha _____

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