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FORMULACIONES FARMACEUTICAS LIQUIDAS DE PALONOSETRON

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Suiza**5****PCT (86)**Solicitud Internacional No. PCT/EP2004/000888Fecha: 30 de enero de 2004Publicación Internacional No. WO 2004/067005 A1Fecha: 12 de agosto de 2004**6****Título (54)****FORMULACIONES FARMACÉUTICAS LÍQUIDAS DE PALONOSETR N****7****Clasificación Internacional (51)** A61K 31/4747 A61P1/08**8****Prioridad**SI ☒ NO ☐

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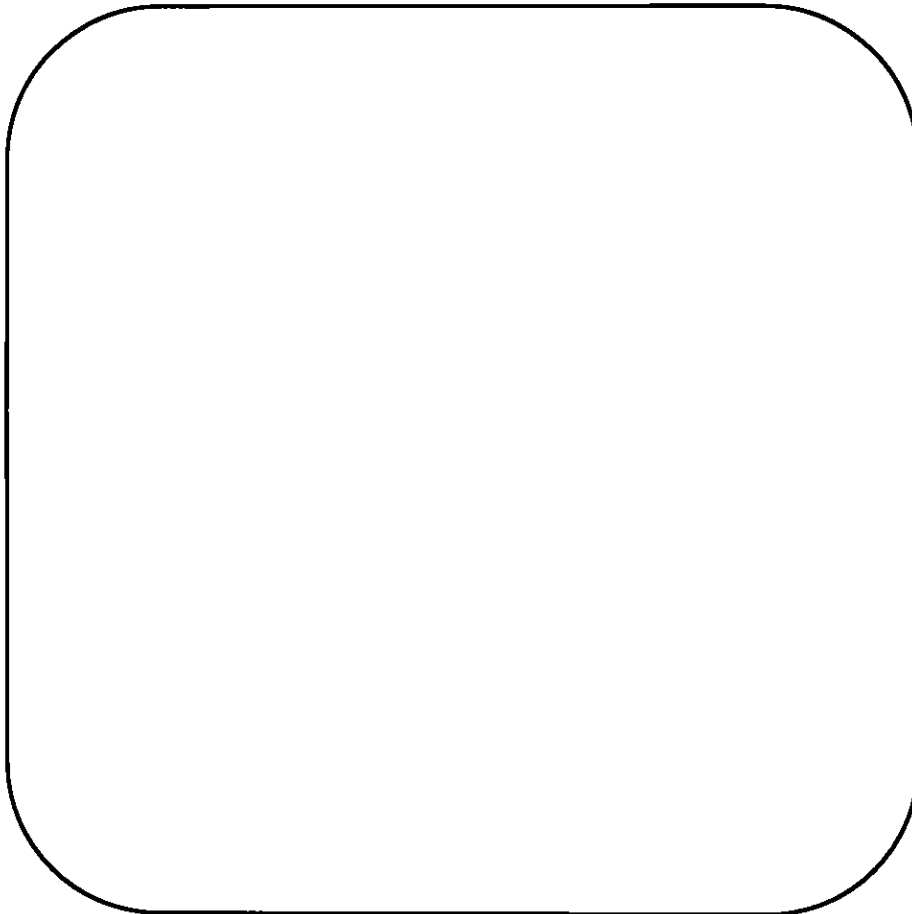
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Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☐ Documento que acredita 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 efectuado por la IPEA.
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- ☐ 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 12x12
- ☐ 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.
- ☒ Otros: **VER HOJA ANEXA**

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

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DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/067005 A1**

Descripción:

Páginas 14 en el idioma original

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2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional y copia de los documentos citados.**
5. ☒ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
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(54) Title: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

(57) Abstract: The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

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LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

FIELD OF THE INVENTION

The present invention relates to shelf-life stable liquid formulations of
5 palonosetron that are especially useful in the preparation of injectable and oral
medicaments.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-
10 operative environments that drastically affects the quality of life of people undergoing
such treatments. In recent years a class of drugs referred to as 5-HT₃ (5-
hydroxytryptamine) receptor antagonists has been developed that treat such emesis by
antagonizing cerebral functions associated with the 5-HT₃ receptor. *See Drugs Acting on*
5-Hydroxytryptamine Receptors: The Lancet Sep. 23, 1989 and references cited therein.
15 Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and
dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before
chemotherapy or radiotherapy is initiated, and can be administered more than once during
a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or
oral elixirs to either supplement an intravenous administration, or to ease home usage of
20 the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods
of several days even when they are administered only once, it would be desirable to
administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk
of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not
25 proven especially helpful meeting this need, however, because the 5-HT₃ receptor
antagonists currently marketed have proven to be less effective in controlling delayed
nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a*
5HT₃ Receptor Antagonist for the Hospital Formulary. EHP, Oct. 1996;2 (suppl 1):S19-
24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ receptor antagonist reported in U.S. Patent No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT₃ receptor antagonists, has a surprising half-life of about 40 hours, and is effective to
5 reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

Ingredient	
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate	q.s. to make Isotonic
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

10

The formulation has a pH of 3.7 and a shelf stability of less than the 1-2 year time period required by health authorities in various countries.

Ondansetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628,
15 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802. Commercially it is distributed by GlaxoSmithKline as Zofran® and is indicated for prevention of postoperative nausea and vomiting (PONV), cancer chemotherapy-induced nausea and vomiting (CINV), and radiotherapy-induced nausea and vomiting (RINV) and it is available as an injection, tablets and solution, and as Zofran ODT® (ondansetron) Orally
20 Disintegrating Tablets.

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Patent Numbers 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is

distributed by Roche Laboratories Inc. as Kytril , indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

Alosetron, its uses, and medicaments made with alosetron are disclosed in U.S. Patent Numbers 5,360,800 and 6,284,770. Commercially it is distributed by GlaxoSmithKline as Lotronex®.

Tropisetron is commercially available as Navoban® (Novartis) CAS - 89565-68-4 (tropisetron); CAS - 105826-92-4 (tropisetron hydrochloride) and it is indicated for treatment of PONV and CINV.

Dolasetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 5,011,846, and 4,906,755. Commercially it is distributed by Aventis Pharmaceuticals Inc. as Anzemet®, indicated for prevention of both PONV and CINV, and it is offered in the form of a tablet or an intravenous solution.

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT₃ receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

It is an object of the present invention to provide a formulation of Palonosetron hydrochloride with increased pharmaceutical stability for preventing and/or reducing emesis.

It is another object of the invention to provide an acceptable range of concentrations which will stabilize a formulation containing Palonosetron hydrochloride.

It is a further object of the invention to provide a formulation of Palonosetron which would allow for prolonged storage.

It is also an object of the invention to provide a formulation of Palonosetron which would allow terminal sterilization.

SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. These formulations are shelf stable for periods greater than 24 months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only $1/10^{\text{th}}$ the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof; from about 10 to about 100 millimoles citrate buffer; and from about 0.005 to about 1.0 mg/ml EDTA.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically

acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol.

DETAILED DESCRIPTION OF THE INVENTION

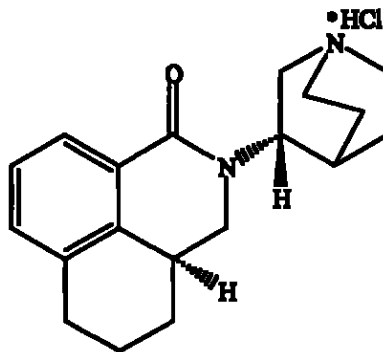
5 DEFINITIONS

"Vial" means a small glass container sealed with the most suitable stopper and seal, other suitable primary containers may be used, for instance, but not limited to, pre-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and non-breakable glass vials, breakable plastic vials, 10 miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of 15 any other element, integer or step, or group of elements, integers or steps

"Palonosetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:

20





Concentrations – When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

5 **"Pharmaceutically acceptable"** means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity.

10 Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid,

15 o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid),

20 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

 In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable

25 inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

DISCUSSION

The fact that palonosetron can be formulated in some instances at concentrations of only about $1/10^{\text{th}}$ the amount of other previously known compounds for treating emesis, surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a
5 pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of
10 palonosetron comprising admixing from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; with a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/mL.

15 A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 mL of
20 solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/mL.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a
25 pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt
30 thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most

optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

5 In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. Similarly, in another embodiment the invention provides a method of formulating a
10 pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. The citrate buffer can be in the form of citric acid and/or a salt of citric acid such as trisodium citrate. In various embodiments, the ranges of one or more of the
15 foregoing ingredients can be modified as follows:

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.

20 • The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.

- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

25 The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the
30 pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly,

in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/mL, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/mL to about 80.0 mg/mL, from about 20.0 mg/mL to about 60.0 mg/mL, or from about 40.0 to about 45.0 mg/mL.

Injectable formulations are typically formulated as aqueous solutions in which water is the primary excipient. Oral formulations will differ from injectable formulations generally by the additional presence of flavoring agents, coloring agents, or viscosity agents. Natural or synthetic sweeteners include, among others, mannitol, sorbitol, saccharose, saccharine, aspartame, acelsulphame K, or cyclamate. These agents are generally present in concentrations in excess of 100 mg/mL or 250 mg/mL when used as sweetening agents, in contrast to the 41.5 mg/mL concentration of mannitol described in some of the embodiments of the invention, in which mannitol is acting simply as a tonicifying agent.

The formulations of the present invention are particularly suited for use in injectable and oral liquid formulations, but it will be understood that the solutions may have alternative uses. For example, they may be used as intermediates in the preparation of other pharmaceutical dosage forms. Similarly, they may have other routes of administration including intranasal or inhalation. Injectable formulations may take any route including intramuscular, intravenous or subcutaneous.

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of

palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18
5 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate
10 buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another
15 embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials); b) filling said containers with a solution of palonosetron in a non-aseptic environment; c) sealing said filled containers; and d) sterilizing said sealed, filled containers, wherein (i) the
20 palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a
25 chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

EXAMPLES**EXAMPLE 1: STABILIZING PH**

A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at 80°C at pH 2.0, 5.0, 7.4, and 10.0.
5 The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

EXAMPLE 2: STABILIZING CONCENTRATION RANGES

A formulation optimization study was performed using an experimental design software. Twenty-four lots of drug product were analyzed to investigate the appropriate concentration ranges for palonosetron hydrochloride (0.05 mg/mL to 5.0 mg/mL), citrate
10 buffer (0 to 80 mM) and EDTA (0 to 0.10%). The level of EDTA and citrate buffer were selected based on the optimal formulation, which was shown to be formulated with EDTA 0.05% and 20 mM citrate buffer at pH 5.0. The results of this study indicated that palonosetron concentration was also a critical factor in chemical stability, with greatest stability seen at the lowest palonosetron concentrations.

15 **EXAMPLE 3: TONICIFYING AGENT**

Formulations of palonosetron hydrochloride in citrate buffer were prepared including either a) sodium chloride or b) mannitol. The palonosetron hydrochloride formulation including mannitol showed superior stability. The optimum level of mannitol required for an isotonic solution was found to be 4.15%.

20 **EXAMPLE 4: FORMULATION I**

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5

EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

* calculated as a free base

EXAMPLE 5: FORMULATION II

The following is a representative pharmaceutical formulation containing palonosetron that is useful for oral formulations, or other liquid formulations of the drug.

5

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	150
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5
Flavoring	q.s.

* calculated as a free base

EXAMPLE 6 – STABILITY OF PALONOSETRON WITHOUT DEXAMETHASONE

The physical and chemical stability of palonosetron HCl was studies in concentrations of 5 µg/mL and 30 µg/mL in 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride injection, and dextrose 5% in lactated Ringer's injection. The admixtures were evaluated over 14 days at 4 °C in the dark and for 48 hours at 23 °C under fluorescent light.

10

Test samples of palonosetron HCl were prepared in polyvinyl chloride (PVC) bags of the infusion solutions at concentrations of 5 and 30 µg/mL. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 5, 7, and 14 days of storage at 4 °C and after 1, 4, 24, and 48 hours at 23 °C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically stable throughout the study. The solution remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl occurred in any of the samples at either temperature throughout the entire study period.

EXAMPLE 7 – STABILITY OF PALONOSETRON WITH DEXAMETHASONE

The physical and chemical stability of palonosetron HCl 0.25 mg admixed with dexamethasone (as sodium phosphate) 10 mg or 20 mg in 5% dextrose injection or 0.9% sodium chloride injection in polyvinyl chloride (PVC) minibags, and also admixed with dexamethasone (as sodium phosphate) 3.3 mg in 5% dextrose injection or 0.9% sodium chloride injection in polypropylene syringes at 4 °C in the dark for 14 days and at 23 °C exposed to normal laboratory fluorescent light over 48 hours, was studied.

Test samples of palonosetron HCl 5 µg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 µg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for

physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4 °C and after 1, 4, 24, and 48 hours at 23 °C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically compatible throughout the study. The solutions remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl and dexamethasone occurred in any of the samples at either temperature throughout the entire study period.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention.

CLAIMS

What is claimed is:

- 1) A pharmaceutically stable solution for preventing or reducing emesis comprising:
 - a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and
 - b) a pharmaceutically acceptable carrier.
- 2) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.02 mg/mL to about 1.0 mg/mL.
- 3) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.03 mg/mL to about 0.2 mg/mL.
- 4) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.
- 5) The solution of claim 1 comprising palonosetron hydrochloride.
- 6) The solution of claim 1 wherein the pH is from about 4.0 to about 6.0.
- 7) The solution of claim 1 wherein the pH is from about 4.5 to about 5.5.
- 8) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises a chelating agent.
- 9) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
- 10) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.
- 11) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.
- 12) The solution of claim 1 adapted for intravenous administration.
- 13) The solution of claim 1 adapted for oral administration.
- 14) A pharmaceutically stable solution for preventing or reducing emesis comprising:

- a) palonosetron or a pharmaceutically acceptable salt thereof; and
 - b) a pharmaceutically acceptable carrier,
- at a pH from about 4.0 to about 6.0.
- 15) The solution of claim 14 wherein the pH is from about 4.5 to about 5.5.
- 5 16) The solution of claim 14 wherein the pH is about 5.0.
- 17) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.
- 18) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.
- 10 19) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises a chelating agent.
- 20) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
- 21) The solution of claim 14 wherein the pharmaceutically acceptable carrier
15 comprises mannitol.
- 22) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer..
- 23) The solution of claim 14 comprising palonosetron hydrochloride.
- 24) The solution of claim 14 further comprising sodium hydroxide or hydrochloric
20 acid.
- 25) The solution of claim 14 adapted for intravenous administration.
- 26) The solution of claim 14 adapted for oral administration.
- 27) A pharmaceutically stable solution for preventing or reducing emesis comprising
- a) from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically
25 acceptable salt thereof;
 - b) from about 10 to about 100 millimoles citrate buffer; and

- c) from about 0.005 to about 1.0 mg/ml EDTA.
- 28) The solution of claim 27 comprising about 0.05 mg/ml to of palonosetron hydrochloride.
- 29) The solution of claim 27 comprising from about 10 to about 40 milliMoles citrate
5 buffer.
- 30) The solution of claim 27 comprising from about 0.3 to about 0.7 mg/ml of EDTA.
- 31) The solution of claim 27 adapted for intravenous administration.
- 32) The solution of claim 27 adapted for oral administration.
- 33) A pharmaceutically stable solution for preventing or reducing emesis comprising
10 a) palonosetron or a pharmaceutically acceptable salt thereof and
b) a pharmaceutically acceptable carrier,
wherein the pharmaceutically acceptable carrier comprises a chelating agent.
- 34) The solution of claim 33 wherein the chelating agent is EDTA.
- 35) The solution of claim 33 wherein the chelating agent is present in an amount from
15 about 0.005 mg/ml to about 1.0 mg/ml.
- 36) The solution of claim 33 wherein the chelating agent is present in an amount from
about 0.3 mg/ml to about 0.7 mg/ml.
- 37) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable
salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.
- 20 38) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable
salt thereof is in a concentration of about 0.05 mg/mL.
- 39) The solution of claim 33 wherein the pharmaceutically acceptable carrier
comprises mannitol.
- 40) The solution of claim 33 wherein the pharmaceutically acceptable carrier
25 comprises from about 10 to about 100 milliMoles of a citrate buffer.
- 41) The solution of claim 33 comprising palonosetron hydrochloride.

- 42) The solution of claim 33 wherein the pH is from about 4.0 to about 6.0.
- 43) The solution of claim 33 wherein the pH is from about 4.5 to about 5.5.
- 44) The solution of claim 33 adapted for intravenous administration.
- 45) The solution of claim 33 adapted for oral administration.
- 5 46) A pharmaceutically stable solution for preventing or reducing emesis comprising
- a) palonosetron or a pharmaceutically acceptable salt thereof and
- b) a pharmaceutically acceptable carrier,
- wherein the pharmaceutically acceptable carrier comprises mannitol.
- 47) The solution of claim 46 wherein the mannitol is in a concentration from about
10 10.0 mg/ml to about 80.0 mg/ml.
- 48) The solution of claim 46 wherein the mannitol is in a concentration from about
40.0 mg/ml to about 45.0 mg/ml.
- 49) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable
salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.
- 15 50) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable
salt thereof is in a concentration of about 0.05 mg/mL.
- 51) The solution of claim 46 wherein the pharmaceutically acceptable carrier
comprises a chelating agent.
- 52) The solution of claim 46 wherein the pharmaceutically acceptable carrier
20 comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
- 53) The solution of claim 46 wherein the pharmaceutically acceptable carrier
comprises from about 10 to about 100 milliMoles of a citrate buffer.
- 54) The solution of claim 46 comprising palonosetron hydrochloride.
- 55) The solution of claim 46 wherein the pH is from about 4.0 to about 6.0.
- 25 56) The solution of claim 46 wherein the pH is from about 4.5 to about 5.5.
- 57) The solution of claim 46 adapted for intravenous administration.

- 58) The solution of claim 46 adapted for oral administration.
- 59) A pharmaceutically stable solution for preventing or reducing drug induced emesis comprising
- a) palonosetron or a pharmaceutically acceptable salt thereof and
- 5 b) a pharmaceutically acceptable carrier,
- wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.
- 60) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 70 milliMoles of a citrate buffer.
- 10 61) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 40 milliMoles of a citrate buffer.
- 62) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.
- 63) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.
- 15 64) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises a chelating agent.
- 65) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
- 20 66) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises mannitol.
- 67) The solution of claim 59 comprising palonosetron hydrochloride.
- 68) The solution of claim 59 wherein the pH is from about 4.0 to about 6.0.
- 69) The solution of claim 59 wherein the pH is from about 4.5 to about 5.5.
- 25 70) The solution of claim 59 adapted for intravenous administration.
- 71) The solution of claim 59 adapted for oral administration.

- 72) A method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising:
- a) providing a room comprising said one or more containers;
 - b) adjusting or maintaining the temperature of the room at greater than about
5 ten degrees celcius;
 - c) storing said containers in said room for one month or more,
- wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about
10 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises mannitol or a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.
- 15 73) A method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising:
- a) providing one or more sterile open containers;
 - b) filling said containers with a solution of palonosetron in a non-aseptic environment
 - 20 c) sealing said filled containers; and
 - d) sterilizing said sealed, filled containers,
- wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about
25 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises mannitol or a

25

chelating agent or mannitol, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RQM01 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.150)
0-5	Petition (The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty)	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	HM 5089-01WO
I	Title of invention	LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	HELSINN HEALTHCARE SA
II-5	Address:	P. O. Box 357 6915 Pambio-Moranco, Lugano Switzerland
II-6	State of nationality	CH
II-7	State of residence	CH
III	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	CALDERARI, Giorgio
III-1-5	Address:	Via Scer 6852 Rancate Switzerland
III-1-6	State of nationality	CH
III-1-7	State of residence	CH

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II-3	Applicant and/or inventor	applicant and inventor US only BONADEO, Daniele Via Ronco Capo Caccia, 32 21030 Casalruigno, Varese Italy IT IT
II-3-1	This person is:	
II-3-2	Applicant for	
II-3-4	Name (LAST, First)	
II-3-5	Address:	
III-3-6	State of nationality	
III-3-7	State of residence	
II-3	Applicant and/or inventor	applicant and inventor US only CARNELLA, Roberta Via Europa, 50 21040 Morazzone, Varese Italy IT IT
II-3-1	This person is:	
II-3-2	Applicant for	
II-3-4	Name (LAST, First)	
II-3-5	Address:	
III-3-6	State of nationality	
III-3-7	State of residence	
II-4	Applicant and/or inventor	applicant and inventor US only BRAGLIA, Enrico Via Pian Scairolo 9 6912 Pazzallo Switzerland CH CH
II-4-1	This person is:	
II-4-2	Applicant for	
II-4-4	Name (LAST, First)	
II-4-5	Address:	
III-4-6	State of nationality	
III-4-7	State of residence	
II-5	Applicant and/or inventor	applicant and inventor US only BRAGLIA, Riccardo Via Pian Scairolo 9 6912 Pazzallo Switzerland CH CH
II-5-1	This person is:	
II-5-2	Applicant for	
II-5-4	Name (LAST, First)	
II-5-5	Address:	
III-5-6	State of nationality	
III-5-7	State of residence	

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Original (for SUBMISSION)

IV-1	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	
IV-1-1	Name (LAST, First)	LEISSLER-GERSTL, Gabriele	
IV-1-2	Address:	Eisenführ, Speiser & Partner Arnulf- strasse 25 80335 München Germany	
IV-1-3	Telephone No.	+49 89 54 90 750	
IV-1-4	Facsimile No.	+49 89 55 02 75 55	
V	DESIGNATIONS		
V-1	The filing of this request constitutes under Rule 4.3(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.		
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	30 January 2003 (30.01.2003)	
VI-1-2	Number	60/444,351	
VI-1-3	Country	US	
VI-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosure or exceptions to lack of novelty	-	

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PCT REQUEST.

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	4	-
IX-2	Description	14	-
IX-3	Claims	7	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	26	
	Accompanying forms	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name:		
X-1-2	Name of signatory		
X-1-3	Capacity		
		LEISSNER-GERSTL, Gabriele	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.150)
0-5	Applicant's or agent's file reference	HM 5089-01WO
2	Applicant	HELSINN HEALTHCARE SA
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (EUR)
12-1	Transmittal fee T	⇒ 100
12-2-1	Search fee S	⇒ 1550
12-2-2	International search to be carried out by	EP
12-3	International filing fee (first 30 sheets) H	902
12-4	Remaining sheets	0
12-5	Additional amount (A) 0	0
12-6	Total additional amount B	0
12-7	H + B =	902
12-12	EASY Filing reduction R	-64
12-13	Total international filing fee (I-R)	⇒ 838
12-14	Fee for priority document Number of priority documents requested	0
12-15	Fee per document (C) 30	
12-16	Total priority document fee: P	⇒
12-17	TOTAL FEES PAYABLE (T+S+B+P)	⇒ 2488
12-18	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions The receiving Office	European Patent Office (EPO) (RO/EP)
12-20-1	Authorization to charge the total fees indicated above.	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-31	Deposit account No.	28 000 148
12-32	Date	29 January 2004 (29.01.2004)
12-33	Name and signature	LEISSLER-GERSTL, Gabriele 

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

PCT

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Original (for SUBMISSION)

13-3-3	Validation messages Names	Green? Applicant 1: Telephone No. missing
	Validation messages Names	Green? Applicant 1: Facsimile No. missing
13-3-7	Validation messages. Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
	Validation messages Contents	Green? The international application contains no drawings. Please verify.
	Validation messages Contents	Green? Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
13-3-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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:
IPEN/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.

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: HM 5089-01WO	
International application No. PCT/EP2004/000888	International filing date (day/month/year) 30.01.2004
(Earliest) Priority date (day/month/year) 30.01.2003	
Title of invention Liquid pharmaceutical formulations of palonosetron	
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.) HELSINN HEALTHCARE SA P.O. Box 357 6915 Pambio-Noranco, Lugano Switzerland	Telephone No.
	Facsimile No.
	Telexprinter No.
	Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
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.) GALDERARI, Giorgio Via Scer 6862 Rancate Switzerland	
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
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.) BONADEO, Daniele Via Ronco Capo Caccia, 32 21030 Casalzuigno, Varese Italy	
State (that is, country) of nationality: IT	State (that is, country) of residence: IT
☒ Further applicants are indicated on a continuation sheet.	

Sheet No. 2

International Application No.
PCT/EP2004/000888

Continuation of Box No. II APPLICANT(S)

If none of the following sub-headers is used, this sheet should not be included in the demand.

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.)*

CANNELLA, Roberto
Via Europa, 50
21040 Morazzone, Varese
Italy

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IT

State (that is, country) of residence:
IT

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.)*

BRAGLIA, Enrico
Via Pian Scalrolo 9
6912 Pazzallo
Switzerland

State (that is, country) of nationality:
CH

State (that is, country) of residence:
CH

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.)*

BRAGLIA, Riccardo
Via Pian Scalrolo 9
6912 Pazzallo
Switzerland

State (that is, country) of nationality:
CH

State (that is, country) of residence:
CH

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.)*

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

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

The following person is ☒ agent ☐ common representativeand ☒ 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: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)LEISSLER-GERSTL Gabriele
Eisenführ, Speiser & Partner
Postfach 31 02 60
D-80102 München

Telephone No.

+49-89-5490 720

Facsimile No.

+49-89-5502 7555

Teleprinter No.

Agent's registration No. with the Office

☐ 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 filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☒ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ 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 the applicable time limit under Rule 49.1(a).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* 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 filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. 4

International application No.
PCT/EP2004/000888

Box No. VI CHECK LIST

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

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

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 listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney, reference number, if any: | 8. ☐ other (specify): |

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).


 Gabriele Leissler-Gerdt, European Patent Attorney

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 time limit 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.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 34bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 34bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 34bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA as:

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

To: EISENFÜHR, SPEISER & PARTNER Attn. Leisler-Gerard G. Arnulfstrasse 21 D-80335 München GERMANY	EISENFÜHR, SPEISER & PARTNER EINGEGANGEN / RECEIVED 05 Mai 2004 NOT MÜNCHEN 06.07.04 NOT 30.11.04
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(PCT Rule 44.1)

Applicant's or agent's file reference EM 5089-01WO	Date of mailing (day/month/year) 06/05/2004
International application No. PCT/EP2004/000888	International filing date (day/month/year) 30/01/2004
Applicant HELGINK HEALTHCARE SA	

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 18:

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 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 18 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 18 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. 5518 Patenteaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-3040, Tlx. 31 551 epo nl, Fax (+31-70) 340-3016	Authorized officer Angela Lopez Navarro
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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 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.

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 25 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 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 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.

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, 16 and 18 replaced by amended claim 14; claim 17 subdivided into amended claims 18, 19 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

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. References 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 Offices, 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 EM 5089-01WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 8 below.	
International application No. PCT/EP2004/000888	International filing date (day/month/year) 30/01/2004	(Earliest) Priority Date (day/month/year) 30/01/2003
Applicant HELSINKI HEALTHCARE SA		

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, see Box No. I.

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

3. ☐ Unity of invention is lacking (see Box 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 36.2(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

International Application No.

PCT/EP2004/000888

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4747 A61K9/08

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.
X	US 5 202 333 A (BERGER JACOB ET AL) 13 Apr11 1993 (1993-04-13) cited in the application column 28, line 59-68; examples 10,11,13	1,2,13
A	TANG J ET AL: "THE EFFICACY OF RS-25259, A LONG-ACTING SELECTIVE 5-HT3 RECEPTOR ANTAGONIST, FOR PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER HYSTERECTOMY PROCEDURES" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 87, no. 2, 1998, pages 462-467, XP009027884 ISSN: 0003-2999 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 raise doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (see specification)
- *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.
- *B* document member of the same patent family

Date of the actual completion of the international search

21 Apr11 2004

Date of mailing of the international search report

06/05/2004

Name and mailing address of the ISA

European Patent Office, P.O. Box 2911 Patentstr. 2
NL - 2200 HV Rijswijk
Tel. (+31-70) 340-0040, Te. 31 021 apo nl
Fax: (+31-70) 340-0010

Authorized officer

Tardi, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STACHER G: "PALONOSETRON HELSINN" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 10, October 2002 (2002-10), pages 1502-1507, XP009027887. ISSN: 0967-8298 the whole document	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 14-71

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely claims 1-13 and 72-73.

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(a) 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.

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:
2. ☒ Claims Nos.: 14-71
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 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.

INTERNATIONAL SEARCH REPORT.

Information on patent family members

International Application No

PCT/EP2004/000888

45

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5202333	A	13-04-1993	AT 124698 T 15-07-1995
			AU 642178 B2 14-10-1993
			AU 6696390 A 06-06-1991
			BR 1100680 A3 08-02-2000
			CA 2030718 A1 29-05-1991
			DE 69020694 D1 10-08-1995
			DE 69020694 T2 18-01-1996
			DK 430190 T3 21-08-1995
			EP 0430190 A2 05-06-1991
			ES 2075121 T3 01-10-1995
			FI 905839 A ,B, 29-05-1991
			HK 36097 A 27-03-1997
			HU 56368 A2 28-08-1991
			IE 904269 A1 05-06-1991
			IL 96486 A 30-03-1995
			IL 110622 A 30-03-1995
			JP 1935956 C 26-05-1995
			JP 3176486 A 31-07-1991
			JP 6062607 B 17-08-1994
			KR 9707917 B1 17-05-1997
			NO 905120 A ,B, 29-05-1991
			NZ 236225 A 25-09-1992
			PL 287961 A1 02-12-1991
			PL 166267 B1 28-04-1995
			PL 166277 B1 28-04-1995
			PT 96001 A ,B 30-09-1991
			ZA 9009529 A 26-08-1992

[34] TRICYCLIC 5-HT₂ RECEPTOR ANTAGONISTS

[75] Inventors: Jacob Berger, Los Altos Hills; Robin D. Clark, Palo Alto; Richard M. Eglen, Mountain View; William L. Smith, Sunnyvale; Klaus K. Weiskardt, San Francisco, all of Calif.

[73] Assignee: Syntex (U.S.A.) Inc., Palo Alto, Calif.

[21] Appl. No.: 704,865

[22] Filed: May 22, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 442,082, Nov. 28, 1989, abandoned.

[51] Int. Cl.³ C07D 471/08; A61K 31/35; A61K 31/435

[52] U.S. Cl. 514/296; 514/211; 514/272; 540/520; 546/99; 546/100

[58] Field of Search 546/99, 100; 540/520; 514/211, 296

[36] References Cited

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3,341,528 8/1967 Shavel, Jr. 546/98
3,596,132 7/1973 Barsness 280/289 R
4,209,543 1/1982 Kocky 546/98
4,571,996 1/1986 Hunt 546/136
4,839,367 9/1990 King et al. 514/243

FOREIGN PATENT DOCUMENTS

0094488 11/1983 European Pat. Off.
430190 6/1991 European Pat. Off.
88-04282 6/1988 World Int. Prop. Cl.

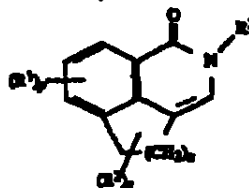
OTHER PUBLICATIONS

Reynolds, J. C. 1989, Prokinetic Agents: A Key in the Future of Gastroenterology, Gastroenterology Clinics of North America, 18:437-457.
1989, Drugs Acting on 5-Hydroxytryptamine Receptors, The Lancet, pp. 717-719.
Scholtysik, G. 1988, 5-Hydroxytryptamine Antagonist JCS 205-930 Blocks Cardiac Potassium, Sodium and Calcium Channels, J. of Pharmacol. Exp. Ther. 243, 3:773-778.
King et al. 1990, Benztropine as "Virtual Ring" Mimics of o-Methoxybenzamide: Novel and Potent 5-HT₂ Receptor Antagonists, J. Med. Chem. 33:2942-2944.
Festfield, R. 1988, Drugs and the treatment of Migraine, Trends Pharmacol. Sci. 9:141-143.
Komatsu et al. 1978, Chem. Abs. 89:100152s.
Hibert et al. 1988, Preparation and testing of 4-(2-pyrimidinyl)-1-piperazinepyrimidinediones and -oxazines as minor tranquilizers, Chem. Abs. 108:221716p.

Primary Examiner—Mark L. Borch
Attorney, Agent, or Firm—Wayne W. Montgomery;
Derek P. Freyberg; Tom M. Moran

[57] ABSTRACT

The present invention is directed to 5-HT₂ receptor antagonist compounds of formula I:



in which the dashed line denotes an optional double bond;

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1 or 2;

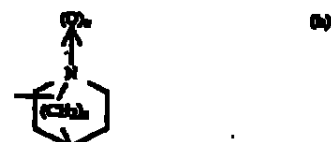
each R¹ is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkoxy)amino;

each R² is lower alkyl; and

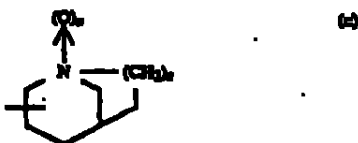
R³ is a group selected from Formulas (a), (b), (c) and (d):



(a)



(b)



(c)



(d)

in which

u is 0 or 1;

z is 1, 2 or 3; and

R⁴ is C₁₋₇ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, or a group (CH₂)_tR⁵ where t is 1 or 2 and R⁵ is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkyl; trifluoromethyl, halogen, nitro, carbonyl, esterified carbonyl, and C₁₋₄ alkyl optionally substituted by hydroxy, C₁₋₄ alkoxy, carbonyl, esterified carbonyl or in vivo hydrolyzable acylonyl; and the pharmaceutically acceptable salts, individual isomers, mixtures of isomers, processes for preparation, compositions, and methods of use thereof.

80 Claims, No Drawings

TRICYCLIC 5-HT₂ RECEPTOR ANTAGONISTS

This application is a continuation-in-part of copending application, Ser. No. 07/442,082, filed Nov. 21, 1989 and now abandoned.

FIELD OF THE INVENTION

This invention relates to novel compounds which are 5-HT₂ receptor antagonists, pharmaceutical compositions containing them and methods for their use and methods for preparing these compounds. In particular, it relates to tricyclic 5-HT₂ receptor antagonists containing a bridged bicyclic amine substituent. The invention also relates to novel intermediates for making the 5-HT₂ receptor antagonists.

BACKGROUND OF THE INVENTION

Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of substantial research. Serotonin, also referred to as 5-hydroxytryptamine (5-HT), acts both centrally and peripherally on discrete 5-HT receptors. 5-HT receptors are presently delineated into three major subclassifications - 5-HT₁, 5-HT₂ and 5-HT₃ - each of which may also be heterogeneous. Receptors of the 5-HT₂ subclass pervade autonomic neurons and appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.

5-HT₂ receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT₂ receptor level, i.e., 5-HT₂ receptor antagonists, possess potent antiemetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy (see *Drugs Acting on 5-Hydroxytryptamine Receptors*, *The Lancet* Sep. 23, 1989 and refs. cited therein).

Functional bowel disorders are prevalent in much of the industrialized world. Chronic gastroesophageal reflux disease alone may be present in as much as 15% of the population. Use of prokinetic agents is one of the most effective methods known for treating such disorders. Because many 5-HT₂ antagonists possess prokinetic properties and are relatively free from side effects they are particularly useful in the treatment of gastrointestinal diseases (see Reynolds R. C. *Prokinetic Agents: A Key in the Future of Gastroenterology*, *Gastroenterology Clinics of North America* 1989, 18, 437-457).

5-HT₂ receptors are present in those areas of the brain which control mood, emotion, reward and memory. 5-HT₂ receptor antagonists reduce mesolimbic dopamine levels, a necessary property for antipsychotic activity. Such antagonists also increase cholinergic tone in the limbic-cortical region, which may explain their cognitive enhancing effects. In addition, 5-HT₂ antagonists possess anxiolytic properties, demonstrate potential for use in the treatment of dependency disorders and are under investigation in patients with schizophrenia (see article from *The Lancet* previously cited).

There is evidence that 5-HT₂ receptors mediate nociceptive input to afferent neurons (see Glenn, E.; Froud-Riz, H. K.; Anderson, E. G. *Neurosci Lett* 1988, 93, 315). 5-HT₂ antagonists may therefore be of value in the control of pain, particularly migraine (see Pentfield R.;

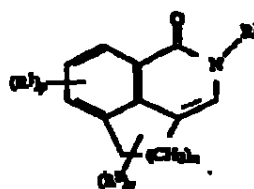
Drugs and the Treatment of Migraine, *Trends Pharmacol Sci* 1988, 9, 141).

The 5-HT₂ receptor antagonist ICH 205-930 inhibits arrhythmias in a variety of animal models and exerts mixed class III and class I antiarrhythmic properties in ventricular myocytes (see Scholtysik, G.; Imoto, Y.; Yatan, A.; Brown, A. M. *J. Pharmacol Exp Ther* 1988, 245, 773 and references therein). 5-HT₂ antagonists may therefore be of use in treating or preventing arrhythmias.

The disclosures of these and other documents referred to throughout this application, e.g., in the Pharmacology section of the Detailed Description of the invention, are incorporated herein by reference.

SUMMARY OF THE INVENTION

The first aspect of this invention is the compounds of Formula I:



in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

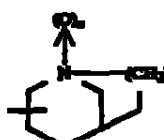
p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each R¹ is independently selected from halogen, hydroxy, lower alkyl, lower alkyl, nitro, amino, amido, carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkyl)amino;

each R² is lower alkyl; and

R³ is a group selected from Formulae (a), (b), (c) and (d):



in which

u is 0 or 1;

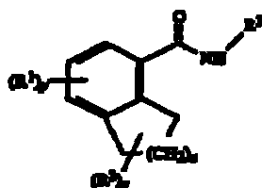
x is 1, 2 or 3; and

R^4 is C_{1-7} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl, or a group $(CH_2)_t R^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally substituted by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally further substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acylonyl; and the pharmaceutically acceptable salts, individual isomers and mixtures of isomers thereof.

A second aspect of this invention is a pharmaceutical composition containing a compound of Formula I in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating diseases involving emesis, gastrointestinal disorders, CNS disorders, cardiovascular disorders or pain by administering a therapeutically effective amount of a compound of Formula I to a subject afflicted with such a condition.

A fourth aspect of this invention is the compounds of Formula II:



in which a , p , q , R^1 , R^2 and R^3 are as defined for Formula I, which are useful intermediates in preparing compounds of Formula I.

A fifth aspect of this invention are the processes for preparing compounds of Formula I and is set forth in the "Detailed Description Of The Invention."

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a straight, branched, or cyclic saturated hydrocarbon radical having from one to the number of carbon atoms designated. For example C_{1-7} alkyl is alkyl having at least one but no more than seven carbon atoms, e.g., methyl, ethyl, *i*-propyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, pentyl, cyclohexyl, heptyl and the like.

"Alkoxy" means the radical $-OR$ wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkoxy includes, e.g., methoxy, ethoxy, *i*-propoxy, *n*-propoxy, *n*-butoxy, pentoxy, hexoxy and the like.

"Alkoxyl" means the radical $-C(O)R$ wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkoxyl includes ethoxyl, propoxyl, *i*-butoxyl, *n*-butoxyl, pentoxyl, hexoxyl and the like.

"Lower" modifies alkyl, alkoxy and alkoxyl and refers to those alkyl radicals or R groups in alkoxy and alkoxyl radicals containing 1 to 6 carbon atoms.

"Halogen" means fluorine, chlorine, bromine, or iodine.

"Esterified carboxy" means the ester group $-COOR$ wherein R is C_{1-4} alkyl.

"In vivo hydrolyzable acylonyl" means a group $-OC(O)R$, wherein R is C_{1-4} alkyl, capable of undergoing enzymatic hydrolysis within a living organism.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes halogen and alkano- or aranesulfonyloxy such as mesyloxy, ethanesulfonyloxy, benzenesulfonyloxy, tosyloxy and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals (e.g., birds and the like).

"Cytotoxic agents" include platinum anti-cancer agents such as cisplatin (cis-diamminedichloroplatinum), as well as non-platinum anti-cancer drugs such as cyclophosphamide (cytotoxin), vincristine (leurocrystine), procarbazine (*N*-(1-methyl-2-hydroxyethyl)-*N*-nitrosourea), methotrexate, fluorouracil, methotrexamine hydrochloride (2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride), dacarbazine, adriamycin, doxorubicin (doxorubicin-D) cytarabine, carmustine, decarbazine, and others listed at page 1143 of the *Journal of Clinical Oncology* 1985; 7(8): 1143.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effect" of such therapy. Thus, "disease" here includes the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents and radiotherapy.

"Evoke", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present and that the description includes both single bonds and double bonds; "optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt" means that the conversion may or may not be carried out in order for the process described to fall within the invention, and the invention includes those processes wherein the compound of Formula I is converted to the salt and those processes in which it is not.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological

activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, benzoic acid, heptanoic acid, cyclopentanecarboxylic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithiolsulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylcyclo[2.2.2]oct-3-ene-1-carboxylic acid, glucosheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, succinic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolicamine, diethanolamine, triethanolamine, tromethamine, N-methylglucosamine and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to the disease yet does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, i.e., arresting its development, or
- (3) relieving the disease, i.e., causing regression of the disease.

Compounds that have identical molecular formulas but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed "isomers". Isomers that differ in the nature or sequence of bonding of their atoms are termed "constitutional isomers". Isomers that differ only in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are mirror images are termed "enantiomers" or sometimes "optical isomers". Stereoisomers that are superimposable upon their mirror images are termed "achiral" and those not superimposable are termed "chiral". A carbon atom bonded to four different groups is termed a "chiral center" or alternatively as "asymmetric carbon".

When a compound has a chiral center, a pair of enantiomers of opposite chirality is possible. An enantiomer can be characterized by the absolute configuration of its chiral center and described by the R- and S-sequencing rules of Cahn and Prelog (i.e., as (R)- and (S)-isomers) or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- and (-)-isomers, respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a "racemic mixture" or "racemate" and may be

described as the (RS)- or (±)-mixture thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 3rd edition March, Jerry, John Wiley and Sons, New York, 1955).

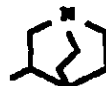
Certain compounds of Formulas I and II can exist as stereoisomers. For example, certain compounds possess a chiral center at the ring carbon of the R³ substituent which is bonded to the amide nitrogen and, when the optional bond is absent, at the 3a-position and therefore can exist as (R)- or (S)-isomers. In addition, certain compounds can exist as the (endo)- or (exo)-isomers, e.g., when the R³ substituent is 1-azabicyclo[3.1.1]non-4-yl.

When a compound of Formula I or II possesses one chiral center, a pair of enantiomers exists. When two chiral centers are present in a compound of Formula I, four separate stereoisomers exist (i.e., two separate pairs of enantiomers). When a compound of Formula I possesses two chiral centers and can exist as endo or exo, eight separate stereoisomers are possible (i.e., two separate pairs of enantiomers in the endo or exo forms).

It is to be understood that when referring to Formula I, II, (a), (b), (c) or (d) in this application, a straight line depicting the covalent bond between the R³ substituent and the amide nitrogen represents the possible geometric isomers and enantiomers or the mixtures, racemic or otherwise, thereof. Similarly, when referring to Formula I in which the optionally bond is absent, a straight line depicting the covalent bond between carbons 3a and 4 represents either the R or S configurations or a mixture racemic, or otherwise, thereof. For purposes of the present application when referring to a compound by name or by formula and the configuration is not designated, it is to be understood that the reference is to all possible forms.

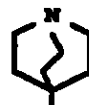
Certain R³ substituents described in this application are of particular interest and are therefore defined specifically as the following:

- (1) Formula (b) where z is 2 and u is 0 having the specific formula



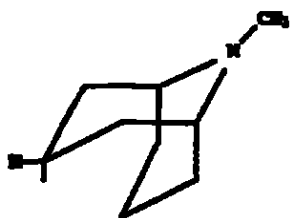
is referred to as 1-azabicyclo[2.2.1]oct-3-yl;

- (2) Formula (b) where z is 2 and u is 0 having the specific formula



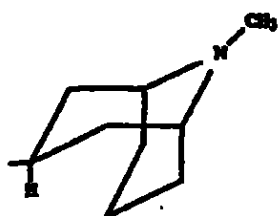
is referred to as 1-azabicyclo[2.2.1]oct-4-yl;

- (3) Formula (a) where z is 3, u is 0 and R⁴ is methyl having the specific formula



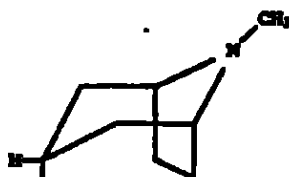
is referred to as (endo)-9-methyl-9-azabicyclo[3.3.1]-non-3-yl;

(4) Formula (a) where z is 3, u is 0 and R^4 is methyl having the specific formula



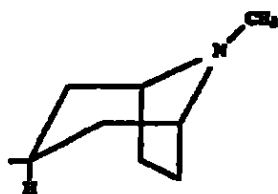
is referred to as (exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

(5) Formula (a) where z is 2, u is 0 and R^4 is methyl having the specific formula



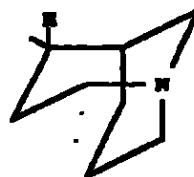
is referred to as (endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

(6) Formula (a) where z is 2, u is 0 and R^4 is methyl having the specific formula



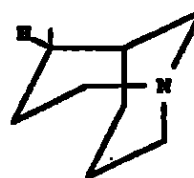
is referred to as (exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

(7) Formula (c) wherein z is 2 and u is 0 having the specific formula



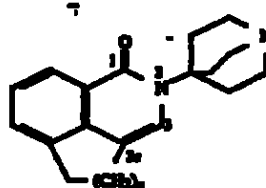
is referred to as (endo)-1-azabicyclo[3.3.1]non-4-yl.

(8) Formula (c) wherein z is 2 and u is 0 having the specific formula



is referred to as (exo)-1-azabicyclo[3.3.1]non-4-yl.

Compounds of Formulas I and II are named in accordance with generally acceptable nomenclature rules established by "Chemical Abstracts." For example, the compound of Formula I in which the optional bond is present, p , q and u are 0 and R^3 is 1-azabicyclo[2.2.2]oct-4-yl:



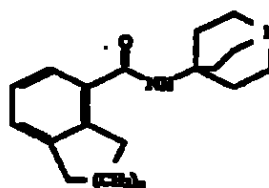
is named

2-(1-azabicyclo[2.2.2]oct-4-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one when n is 1;

2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one when n is 2; and

2-(azabicyclo[2.2.2]oct-4-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one when n is 3.

The compound of Formula II in which the optional bond is present, p , q and u are 0 and R^3 is 1-azabicyclo[2.2.2]oct-4-yl:



is named

N-(1-azabicyclo[2.2.2]oct-4-yl)-4-indracarboximide when n is 1;

N-(1-azabicyclo[2.2.2]oct-4-yl)-4,6,7,8-tetrahydro-1-naphthalenecarboximide when n is 2; and

N-(1-azabicyclo[2.2.2]oct-4-yl)-3,4,7,8-tetrahydro-5H-benzocycloheptene-1-carboxamide when n is 3.

PRESENTLY PREFERRED EMBODIMENTS

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formulas I and II are preferred. For example, preferred compounds of Formula I are those in which both q and u are 0, p is 1, or 2, each R¹ is independently selected from halogen, lower alkoxy or amino, and R⁴ is lower alkyl.

Of particular interest are those compounds of Formula I in which each p, q and u are 0, R⁴ is methyl, and R³ is one of the following groups:

1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
endo-1-azabicyclo[3.3.1]non-4-yl; or
exo-1-azabicyclo[3.3.1]non-4-yl.

Of most interest are the compounds of Formula I in which each p, q and u are 0, and R³ is 1-azabicyclo[2.2.2]oct-3-yl, in particular wherein one or, when present, both chiral centers possess S configurations.

Preferred compounds of Formula II are those in which both p and q are 0, p is 0, 1, or 2, each R¹ is independently selected from halogen, lower alkoxy or amino, and R⁴ is lower alkyl.

Of particular interest are those compounds of Formula II in which each p, q, and u are 0, R⁴ is methyl, and R³ is one of the following groups:

1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
endo-1-azabicyclo[3.3.1]non-4-yl; or
exo-1-azabicyclo[3.3.1]non-4-yl.

Of most interest are compounds of Formula II in which each p, q, and u are 0, and R³ is 1-azabicyclo[2.2.2]oct-3-yl, in particular the S-isomers thereof.

It is understood that these compounds of Formula II of special interest are particularly useful in the synthesis of preferred compounds of Formula I.

UTILITY

Compounds of Formula I exhibit utility in treating a broad range of diseases in animals, particularly humans. Examples of diseases that may be treated using the compounds of Formula I include emesis, gastrointestinal disorders, central nervous system (CNS) disorders, cardiovascular disorders or pain.

Compounds of Formula I are useful in the prevention and treatment of emesis. Causes of such emesis include surgical anesthesia, psychological stress, pregnancy, certain disease states, radiotherapy, radiation poisoning and toxic substances. Disease states which are known to induce emesis include conditions such as gut obstruction, raised intracranial pressure, acute myocardial infarction, migraine headaches and adrenal crisis. Toxic substances which induce emesis include toxins in the form of abnormal metabolites or abnormal accumulation of natural occurring substances associated with such conditions as hepatic coma, renal failure, diabetic ketoacidosis, hyperthyroid crisis, both hypo- and hyper-

parathyroidism and Addison's disease. Emesis may also be caused by ingested toxins, e.g., enterotoxins in staphylococcus-contaminated foods, or by drugs administered for therapeutic purposes, e.g., digitalis, emetine and chemotherapeutic agents.

Compounds of Formula I are of particular value in treating (especially preventing) the emesis induced by radiation poisoning, treatment for cancer with radiotherapy or chemotherapy with cytotoxic agents or drug therapy in general wherein a significant side effect is emesis, e.g., amphotericin B in treating immunosuppressed patients, zidovudine (AZT) in the treatment of AIDS and interferon in treating cancer.

Compounds of Formula I are useful as prokinetic agents in the treatment of gastrointestinal diseases, i.e., diseases of the stomach, esophagus and of both the large and small intestines. Examples of specific diseases include, but are not limited to, dyspepsia (e.g., non-ulcer dyspepsia), gastric stasis, peptic ulcer, reflux esophagitis, flatulence, bile reflux gastritis, pseudo-obstruction syndrome, irritable colon syndrome (which may result in chronic constipation and diarrhea), diverticular disease, biliary dyskinesia (which may result in sphincter of Oddi dysfunction and "sludge" or microscopic crystals in the gall bladder), gastroparesis (e.g., diabetic, postsurgical or idiopathic), irritable bowel syndrome and retarded gastric emptying. The compounds of Formula I are also useful as short-term prokinetics to facilitate diagnostic radiology and intestinal intubation. In addition, the compounds are useful for treating diarrhea, particularly diarrhea induced by cholera and enteric acid syndrome.

Compounds of Formula I are useful in treating diseases of the central nervous system. Categories of such diseases include cognitive disorders, psychosis, obsessive/compulsive and anxiety/depression behavior. Cognitive disorders include attentional or memory deficit, dementia states (including senile dementia of the Alzheimer's type and aging), cerebral vascular deficiency and Parkinson's disease. Psychoses that are treatable using the compounds of Formula I include paranoia, schizophrenia and autism. Obsessive/compulsive behavior that is treatable using compounds of Formula I includes eating disorders, e.g., bulimia, a condition in which an abnormal and constant craving for food is present.

Representative, treatable anxiety/depressive states include anticipatory anxiety (e.g., prior to surgery, dental work, etc.), depression, mania, seasonal affective disorder (SAD), and the convulsions and anxiety caused by withdrawal from addictive substances such as opiates, benzodiazepines, nicotine, alcohol, cocaine and other drugs of abuse.

Compounds of Formula I are useful in the treatment of cardiovascular diseases. Such diseases include arrhythmias and hypertension.

It is thought that 5-HT₃ antagonists prevent certain adverse nervous transmissions and/or prevent vasodilation and are therefore of value for reducing perceived levels of pain. Compounds of Formula I are, therefore, useful in treating pain such as that associated with cluster headaches, migraines, trigeminal neuralgia and visceral pain (e.g., that caused by abnormal distension of hollow visceral organs).

In summary, an aspect of this invention is a method for treating an animal, particularly a human, exhibiting a disease involving emesis, a gastrointestinal disorder, a CNS disorder, a cardiovascular disorder or pain by

administering a therapeutically effective amount of a compound of Formula I to such animal.

Pharmacology

5-HT₂ Receptor binding affinity is measured at 5-HT₂ receptors in membranes prepared from the cerebral cortex of rat brains, as accepted *in vitro* assay (e.g., see Kilpatrick, G. J.; Jones, R. J.; Tyers, M. B. *Nature* 1987, 330, 24-31). The 5-HT₂ receptor binding assay is described in Example 14. The compounds of Formula I exhibit affinity for the 5-HT₂ receptor in this assay.

5-HT₂ receptor antagonist activity is measured by the ability of compounds to inhibit the von Bezold-Jarisch reflex in anesthetized rats, as accepted *in vivo* assay (e.g., see Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tyers, M. B. *Brit. J. Pharmacol.* 1988, 94, 397-412; Cohen, M. L.; Bloomquist, W.; Glida, J. S.; Laceyfield, W. J. *Pharmacol. Exp. Ther.* 1989, 248, 197-201; Ford, J. R. *Arch. Pharmacol.* 1984, 326, 36-46). The 5-HT₂ receptor antagonist assay is described in Example 15.

Anti-emetic activity is determined by measuring reduction of cisplatin-induced emesis in ferrets, as accepted assay (e.g., Costall, B.; Domeney, A. M.; Naylor, R. J.; Tattersall, F. D. *Neuropharmacology* 1984, 23(3), 939-941; Miner, W. D.; Sanger, G. J. *Brit. J. Pharmacol.* 1984, 88, 497-499). The ferret, anti-emetic assay is described in Example 16.

Anti-emetic activity is also determined by measuring reduction of cisplatin-induced emesis in dogs, as accepted assay (e.g., see Smith, W. L.; Alpha, R. S.; Jackson, C. B.; Sancliffo, L. F. *J. Pharm. Pharmacol.* 1989, 41, 101-105; Gylys, J. A. *Rev. Commun. Chem. Pathol. Pharmacol.* 1979, 13(1), 61-68). The dog, anti-emetic assay is described in Example 17.

Prokinetic activity is determined by measuring the rate of gastric emptying after oral administration of test meal to rats, as accepted *in vivo* assay (e.g., see Droppleman, D.; Gregory, R.; Alpha, R. S. *J. Pharmacol. Methods* 1980, 4(3), 227-30). The prokinetic assay is described in Example 18.

Anxiolytic activity is determined by the air-recognized Crawley and Goodwin two-compartment exploratory model (e.g., see Keffel, T.; Michel, A.; Montgomery, D.; Whiting, R. L.; *Neuropharmacology* 1983, 28(3), 901-905). In brief, the method involves determining whether a compound reduces the natural anxiety of mice in a novel, brightly lighted area. The anxiolytic behavior assay is described in Example 19.

Anxiolytic activity during withdrawal from drugs of abuse is determined by the mouse, withdrawal anxiety test, as accepted assay (e.g., see Carboni, E.; Anquet, E.; Leone, P.; Perezzi, L.; Di Chiara, G. *Eur. J. Pharmacol.* 1988, 151, 159-160). This procedure utilizes the exploratory model described above to test for anxiolytic activity after chronic administration and subsequent abrupt cessation of ethanol, diazepam, cocaine or nicotine treatments. The withdrawal anxiety assay is described in Example 20.

Cognition enhancing activity is determined by the mouse, habituation/cognitive enhancement test (e.g., see Barnes, J. M.; Costall, B.; Kelly, M. E.; Naylor, F. J.; Onalvi, E. S.; Tomkins, D. M.; Tyers, M. B. *Br. J. Pharmacol.* 1989, 98, 693P). This procedure utilizes the exploratory model described above to test for improvements in the impaired cognitive performance of aged mice. The cognitive enhancement assay is described in Example 21.

Administration and Pharmaceutical Composition

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another compound of Formula I or with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Therapeutically effective amounts of compounds of Formula I may range from approximately 1.0 microgram per Kg (ug/Kg) body weight per day to 1.0 mg/Kg body weight per day. Preferably the amount will be approximately 10 ug/Kg/day to 0.1 mg/Kg/day. Therefore, a therapeutically effective amount for a 70 Kg human may range from 70 ug/day to 70 mg/day, preferably 700 ug/day to 7.0 mg/day.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease.

In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, emulsions, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, milk, rice, flour, chalk, effervescent gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

Compressed gases may be used to disperse the compound of Formula I in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, nitrous oxide, etc. Other suitable pharmaceutical carriers and their formulations are described in A. R. Albano 1985, *Remington's Pharmaceutical Sciences*, 17th ed. Easton, Pa.: Mack Publishing Company.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w, with the remainder being the excipient or excipients.

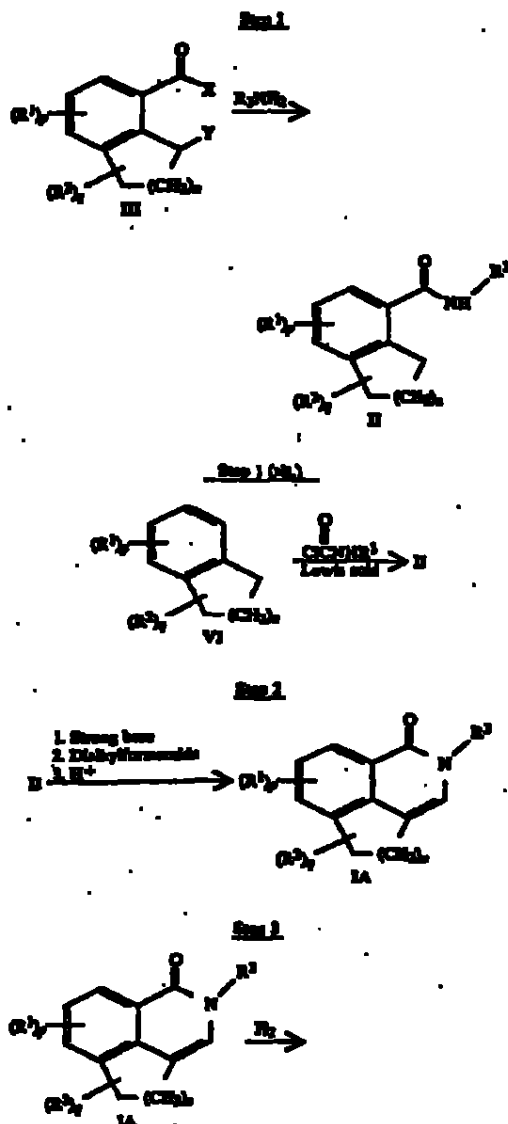
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Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form as libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 11.

Processes for Preparing Compounds of the Invention

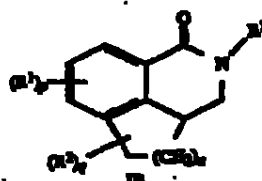
Compounds of Formula I are prepared by the reaction sequence shown below in Reaction Scheme I.

Reaction Scheme I



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continued
Reaction Scheme I



in which X is hydroxy, alkoxy or halogen and Y is hydrogen or X and Y together are oxo, and a, p, q, R^1 , R^2 and R^3 are as defined in the Summary of the Invention with the processes applying particularly well to the presently preferred embodiments.

Scheme I

Compounds of Formula I are conveniently prepared by a two step synthesis comprising (1) converting an acid or acid derivative of Formula III or a fused-ring bicyclic compound of Formula VI to a substituted amide of Formula II and (2) reacting the amide with a formylating agent in the presence of a strong base and then acidifying to form a compound of Formula IA (a compound of Formula I in which the optional bond is present). Compounds of Formula IB (compounds of Formula I in which the optional bond is absent) are subsequently prepared by reduction.

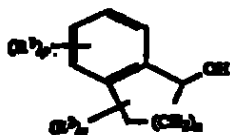
Step 1

Compounds of Formula II are prepared by reacting a compound of Formula III with a substituted amine of the formula NH_2R^3 in which R^3 is as defined in the Summary of the Invention. Reaction conditions are those standard for amide formation (e.g., see *Advanced Organic Synthesis* March 1983, 3rd Ed., 370-376). Generally the reaction is carried out at 20° C. to 200° C., preferably -10° C. to 20° C., and ambient pressure for 0.5 to 3 hours in a suitable inert organic solvent (e.g., methylene chloride, THF and toluene). The conversion of a compound of Formula III in which X is alkoxy to the corresponding amide of Formula II is described in Example 2. The conversion of a compound of Formula III in which X is hydroxy to the corresponding amide of Formula II is described in Example 3. The conversion of a compound of Formula III in which X and Y together are oxo to the corresponding amide of Formula II is described in Example 4.

Alternatively, compounds of Formula II may be prepared by Friedel-Crafts acylation in which a chloroformamide of the formula $ClC(O)NHR^3$ is reacted with a compound of Formula VI in the presence of a Lewis acid such as aluminum chloride, boron trifluoride, hydrogen fluoride or phosphoric acid.

In general, the starting materials utilized in the preparation of compounds of Formula II are known to or can readily be synthesized by those of ordinary skill in the art. For example, the compounds of Formula III where X is hydroxy, p is 1, R^1 is methoxy (particularly meta to the acid), q is 0 and a is 1 or 2 are discussed by Lowenthal, H. J.; Schatzmiller, S. *J. Chem. Soc. Perkin Trans. 1* 1976; 944. Unsubstituted compounds (i.e., wherein p and q are both 0) in which a is 1, 2 or 3 are readily available or may be prepared in accordance with methods known in the art.

Compounds of Formula III wherein X and Y are together one and n is 1, 2 or 3 can be prepared from an alcohol of the formula



in which n, p, q, R¹ and R² are as defined in the Summary of the Invention by treating with a strong base (e.g., n-butyllithium) in an inert organic solvent (e.g., hexanes) for approximately 20 hours followed by bubbling through with carbon dioxide for approximately 5 hours. The preparation of a compound of Formula III in which X and Y together are one is described in Example 1.

Other starting materials that are useful for preparing compounds of the invention are 1-cyano-4-alkoxynaphthalenes which can be hydrolyzed and reduced to the corresponding starting acid of Formula III wherein X is hydroxy, R is 4-alkoxy, q is 0 and n is 2. Halogen-substituted tetralones are well known and are prepared from o-halophenylbutyric acids. These tetralones can be reduced to the appropriate alcohol, converted to an acid and reacted with the R²NH₂ compound as a ketone to form an amide of Formula II.

Step 2

Compounds of Formula IA are prepared by reacting amides of Formula II with a dialkylformamide in the presence of a strong base and then acidifying. The reaction is carried out in a inert etheral solvent (e.g., diethyl ether, dioxane or tetrahydrofuran (THF), preferably THF) at temperatures ranging from -70° C. to 25° C., preferably -20° C. to 0° C., at ambient pressure and under an inert atmosphere (e.g., argon or nitrogen, preferably nitrogen). The dialkylformamide, preferably dimethylformamide (DMF), is generally used in molar excess relative to the amide of Formula II. Any strong base, such as a Grignard reagent or an appropriate alkyl lithium, preferably n-butyllithium, can be utilized. Step 2 of Scheme I is described in Examples 6, 7, 8 and 9.

Compounds of Formula IB may be prepared by reduction of the corresponding compound of Formula IA. The reduction is carried out under standard hydrogenation conditions with an appropriate hydrogenation catalyst and in a suitable polar, organic solvent. Reaction pressures may vary from atmospheric to approximately 15 megapascals (mPa) and temperatures may range from ambient to approximately 100° C. While any standard catalyst (e.g., rhodium on alumina, etc.) may be used, certain catalysts are preferred. Preferred catalysts include 10% palladium hydride, 20% palladium hydride on carbon, Pearlman's catalyst (50% H₂O-20% palladium content) and palladium/BaSO₄. Suitable solvents include ethanol, DMF, acetic acid, ethyl acetate, tetrahydrofuran, toluene, and the like.

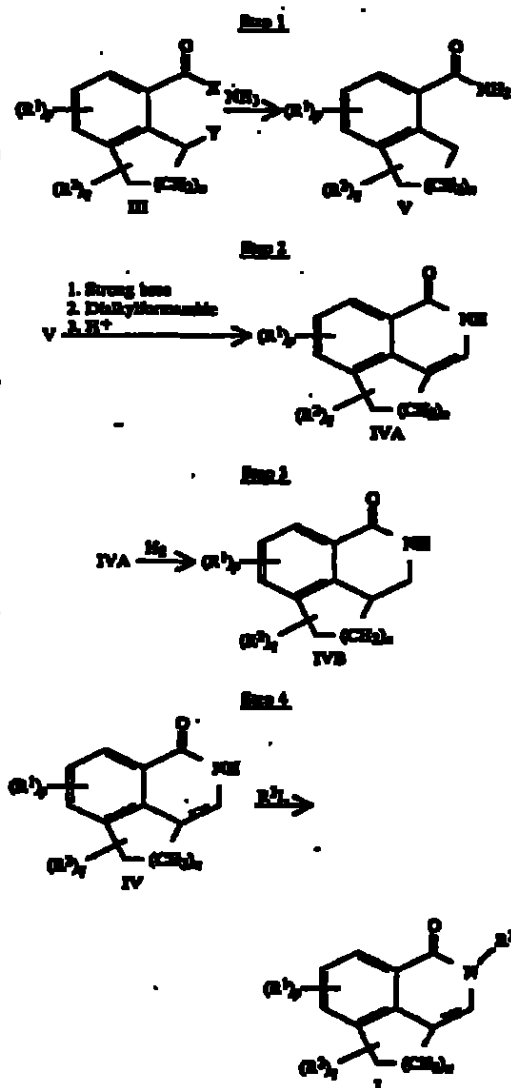
Depending upon the catalyst, solvent, pressure and temperature chosen, the reduction process may take from a few hours to a few days to complete. As an example, a reaction carried out with 20% palladium hydride in acetic acid and 70% perchloric acid at 15 kPa and 85° C. takes approximately 24 hours for full reduction to occur. The reduction of a compound of

Formula IA to a compound of Formula IB is described in detail in Example 10.

A compound of Formula IA can be reduced in either the nonsalt or salt form. If an optically active reagent is employed to form the salt of a compound of Formula IA, formation of one enantiomer over the other may be favored.

Compounds of Formula I are also prepared by the reaction sequence shown below in Scheme II.

Scheme II



in which X is hydroxy, alkoxy or halogen and Y is hydrogen or X and Y together are one, L is a leaving group and n, p, q, R¹, R² and R³ are as defined in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

Scheme II

Alternatively, compounds of Formula I are prepared by a three step synthesis comprising (1) converting an acid or acid derivative of Formula III to an unsubstituted amide of Formula V, (2) reacting the amide with a formylating agent in the presence of a strong base and then acidifying to form a compound Formula IVA (a compound of Formula IV in which the optional bond is present), (3) optionally reducing a compound of Formula IVA to a compound of Formula IVB (a compound of Formula IV in which the optional bond is absent) and (4) condensing the compound of Formula IV with an appropriate alkylating agent to form a compound of Formula I.

Step 1

Compounds of Formula V are prepared by proceeding as in Step 1 of Scheme I but replacing the substituted amine with ammonia.

Step 2

Compounds of Formula IVA are prepared by proceeding as in Step 2 of Scheme I but substituting a compound of Formula V for the compound of Formula II. Compounds of Formula IVB may be prepared by proceeding as described above for the hydrogenation of a compound of Formula IA but substituting a compound of Formula IVA.

Step 3

Compounds of Formula I are prepared by reacting, in the presence of a strong base, a compound of Formula IV with an alkylating agent of the formula R^1L in which R^1 is as defined in the Summary of the Invention and L is a leaving group. The reaction is carried out under standard amide alkylating conditions (Loh, T.; Fung, S. H. *Synth. Commun.* 1979, 9, 797) in an inert solvent at a reaction temperature of 20° C. to 100° C. Appropriate bases include sodium or sodium hydride and are usually employed in molar excess. Suitable solvents include tetrahydrofuran or *N,N*-dialkylformamides such as *N,N*-dimethylformamide.

Alternatively, alkylation may be accomplished via phase-transfer catalyst (PTC) techniques. Such techniques comprise carrying out the reaction in the presence of catalyst and in a liquid-liquid two phase solvent system (Gajda, T.; Zwierzak, A. *Synthesis, Communications* 1981, 1005), or preferably, in a solid-liquid system (Yamswald, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* 1981, 1143; Koskela, A.; Zdzienicki, S.; Zwierzak, A. *Synthesis* 1978, 527, 549).

A liquid-liquid two-phase system is comprised of an aqueous phase consisting of a concentrated alkali hydroxide solution (e.g., 50% aqueous sodium hydroxide), an organic phase comprised of an inert water-immiscible organic solvent solvent, and an appropriate catalyst. A solid-liquid system consists of a powdered alkali hydroxide/alkali carbonate suspended in an organic solvent and catalyst.

The reaction is effected by adding slowly to a PTC system containing a compound of Formula IV an alkylating agent of the formula R^1L until 10 to 50% in excess. The reaction mixture is kept at reflux until the reaction is complete. The mixture is then cooled to room temperature and the compound of Formula I is isolated by conventional methods. Suitable organic solvents include benzene, toluene, and the like. Appro-

priate catalysts include aluminas coated with potassium fluoride and quaternary ammonium sulfates such as tetra-*n*-butyl-ammonium hydrogen sulfate and triethylmethylammonium chloride.

A variation of Scheme II comprises converting a compound of Formula V to a compound of Formula II by one of the above described alkylation processes and then proceeding as in Step 2 of Scheme I to form a compound of Formula I.

Additional Processes

Compounds of Formula I in which substituent R^1 is NH_2 may be prepared by the reduction of a nitro substituent on the corresponding compound of Formula I; in which R^1 is alkoxy or dialkylamino, by substitution of a corresponding nitro or halo substituent; or in which R^1 is hydroxy, by the de-alkylation of a corresponding alkoxy substituent. Furthermore, compounds of Formula I in which R^1 is Cl , Br , I or NO_2 may be prepared by the introduction of such substituent onto a ring activated by an already present R^1 substituent such as NH_2 , NHR , NR_2 , OH or alkoxy; or in which R^1 is an aceto-amido substituent, by the acylation of a corresponding amino substituent. All of the additional processes described above may be performed by methods well known to one of ordinary skill in the art of organic synthesis.

Compounds of Formula I in which n is 1 (compounds of Formula I in which the cyclic amine portion of R^2 is in the *N*-oxide form) may be prepared by oxidation of the corresponding compound of Formula I in which n is 0, preferably the oxazolid form. The oxidation is carried out at a reaction temperature of approximately 0° C. with an appropriate oxidizing agent and in a suitable inert, organic solvent. Suitable oxidizing agents include peroxy acids such as trifluoroperoxyacetic acid, permaleic acid, perbenzoic acid, peracetic acid, and *m*-chloroperoxybenzoic acid. Suitable solvents include halogenated hydrocarbons, e.g., dichloromethane. The oxidation of a compound of Formula I in which n is 0 to the corresponding *N*-oxide is described in Example 12. Alternatively, the compounds of Formula I in which n is 1 may be prepared using *N*-oxide derivatives of the starting materials or intermediates, which may be prepared in a similar manner.

Compounds of Formula I in which n is 0 (compounds of Formula I wherein the cyclic amine portion of R^2 is not in the *N*-oxide form) are also prepared by reduction of the corresponding compound of Formula I in which n is 1. The reduction is carried out under standard conditions with an appropriate reducing agent in a suitable solvent. The mixture is occasionally agitated while the reaction temperature is gradually increased over a range of 0° C. to 50° C. Appropriate reducing agents include sulfur, sulfur dioxide, triaryl phosphines (e.g., triphenyl phosphine), alkali borohydrides (e.g., lithium borohydride, sodium borohydride, etc.), phosphorus trichloride and trihydride. Suitable solvents include acetonitrile, ethanol or aqueous dioxane.

As will be apparent to one of ordinary skill in the art, compounds of Formula I may be prepared as individual isomers or mixtures of isomers. Isomers which are diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are readily separated by taking advantage of these differences. For example, diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in

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solubility. The separation of a single diastereomer of Formula I is described in Example 13.

Optical isomers can be separated by reacting the racemic mixture with an optically active resolving agent to form a pair of diastereomeric compounds. The isomers are then separated by any of the techniques described above for the separation of diastereomers and the pure optical isomer recovered, along with the resolving agent, by any practical means that would not result in racemization. While resolution of optical isomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred, e.g., crystalline diastereomeric salts. Suitable resolving acids include tartaric acid, o-nitrotartaric acid, mandelic acid, maleic acid, the 2-arypropionic acids in general, and camphorsulfonic acid.

Individual isomers of compounds of Formula I can also be separated by such methods as direct or selective crystallization or by any other method known to one of ordinary skill in the art. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds of Formula I can be found in Jean Jacques, Andre Collet, Samuel H. Wilen *Enantioselective Reactions and Resolution* 1981, John Wiley & Sons, Inc. Alternatively, individual isomers of compounds of Formula I can be prepared using the homeric forms of the starting materials.

Compounds of Formula I are be converted to the corresponding acid addition salt with a pharmaceutically acceptable inorganic or organic acid. In addition, pharmaceutically acceptable salts may be formed when the acidic proton of R¹ hydroxy substituents present are capable of reacting with inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application.

Compounds of Formula I in the acid addition salt form are converted to the corresponding free base by treatment with a suitable base such as ammonium hydroxide solution, sodium hydroxide or the like. Compounds of Formula I in which R¹ hydroxy substituents form salts are converted to the corresponding free base by treatment with a suitable acid such as hydrochloric acid.

Of the two processes for synthesizing compounds of Formula I described within this application, Scheme I is preferred. While compounds of Formula I may be synthesized by the process described in Scheme II, the alkylation step therein may require severe reaction conditions and is usually restricted to alkylation of unsubstituted amides with primary alkylating agents, e.g., CH₃I.

In summary, the processes for preparing the compounds of Formula I are:

- (1) reacting a compound of Formula II with a formylating agent in the presence of a strong base and then acidifying to form a compound of Formula IA or reacting a compound of Formula IV with an alkylating agent of the formula R²X to form a compound of Formula I;
- (2) optionally hydrogenating a compound of Formula IA to form a compound of Formula IB;
- (3) optionally reacting with or exchanging substituents present on a compound of Formula I to form an additional substituted compound of Formula I;

(4) optionally converting a salt of a compound of Formula I to the corresponding compound of Formula I;

(5) optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt;

(6) optionally oxidizing a compound of Formula I in which u is 0 to form the corresponding N-oxide;

(7) optionally reducing the N-oxide of a compound of Formula I to the corresponding compound of Formula I in which u is 0; or

(8) optionally separating a mixture of isomers of a compound of Formula I into a single isomer.

In any of the above last step processes, a reference to Formula I, IA, IB, II or IV refers to such Formulas wherein n, p, q, R¹, R², R³, R⁴, R⁵, u, x, y, and z are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

EXAMPLE 1

2,4,7,8,9,9a-Hexahydrocyclohept[cd]isobenzofuran-2-one

The following is the preparation of a compound of Formula III in which

n is 3;

both p and q are 0; and

X and Y are together con.

A solution of n-butyllithium/hexanes (2.5M, 32.0 mL, 80.0 mmol) was added in a dropwise fashion over five minutes to a heated solution of 5,6,7,8-tetrahydro-9H-benzocyclohepten-9-ol (4.03 g, 31.9 mmol) in hexane (100 mL). The mixture was maintained at reflux temperature and stirred for 20 hours. The mixture was then cooled to 10° C. and dry carbon dioxide was bubbled through for 5 hours, during which time a white precipitate formed. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate. The aqueous solution was adjusted to pH 2.0 with concentrated hydrochloric acid while being stirred in an ice-water bath. The resulting precipitate was filtered and recrystallized from hexane to give

2,4,7,8,9,9a-hexahydrocyclohept[cd]isobenzofuran-2-one (2.63 g), m.p. 84°-85° C.

EXAMPLE 2

(8S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indanecarboxamide

The following is the preparation of a compound of Formula II via Scheme 1, Step 1 in which

n is 1;

p and q are 0; and

R³ is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (8S)-3-amino-1-azabicyclo[2.2.2]octane (1.51 g, 12 mmol) in toluene (20 mL) was added dropwise to a stirred solution of trimethylaluminum (12 mmol) in toluene (5 mL), so that the temperature did not exceed 10° C. The mixture was stirred for 30 minutes, and a solution of ethyl 4-indanecarboxylate (2.16 g, 11.5 mmol) in toluene (20 mL) was gradually added. The reaction mixture was heated under reflux for 16 hours, then cooled to room temperature. The reaction mixture was added at 0° C. to aqueous hydrochloric acid (10%, 20 mL). After separation of the layers, the aqueous layer was made basic with 10N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous potassium car-

bonate, filtered and evaporated to give 2.42 g (79%) of a white solid. A sample recrystallized from ethyl acetate gave (R,S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indanecarboxamide, m.p. 158°-154.5° C. Anal. Calcd. for $C_{17}H_{23}N_2O_2$: C, 75.52; H, 6.20; N, 10.36. Found: C, 75.2; H, 6.22; N, 10.50.

Proceeding as in Example 2, but replacing (R,S)-3-amino-1-azabicyclo[2.2.2]octane with (R)-3-amino-1-azabicyclo[2.2.2]octane gave (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indanecarboxamide.

Proceeding as in Example 2, but replacing (R,S)-3-amino-1-azabicyclo[2.2.2]octane with (S)-3-amino-1-azabicyclo[2.2.2]octane gave (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indanecarboxamide, m.p. 159°-160° C; $[\alpha]_D^{25} -47.5^\circ$ ($c=0.4$, $CHCl_3$).

Proceeding as in Example 2 the following are prepared:

N-(1-azabicyclo[2.2.2]oct-4-yl)-4-indanecarboxamide;
N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-4-indanecarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indanecarboxamide;

N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indanecarboxamide;

N-(endo-1-azabicyclo[3.3.1]non-4-yl)-4-indanecarboxamide;

(R,S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide;

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide; and

(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-5-methoxycarboxamide.

EXAMPLE 3

(R,S)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 2;

p and q are 0; and

R¹ is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid (Ofoss-Amate, K. and Stock, L. M., *J. Org. Chem.* 1984; 51: 3432) (2.04 g, 11.7 mmol), oxalyl chloride (1 mL, 11.7 mmol), and dimethylformamide (0.1 mL) in dichloromethane (20 mL) was stirred at room temperature for one hour. The mixture was then concentrated under reduced pressure, and the residue was dissolved in dichloromethane (20 mL). The resulting solution was added dropwise at 0° C. to a solution of (S)-3-amino-1-azabicyclo[2.2.2]octane (1.48 g, 11.7 mmol) in dichloromethane (20 mL). The solution was stirred at room temperature for 30 minutes, and the solvent was evaporated under vacuum. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was basified with NH_4OH and extracted with dichloromethane. The dichloromethane was dried with anhydrous potassium carbonate, filtered and then evaporated to afford 2.73 g of white crystals. A sample recrystallized from ethyl acetate/hexane gave (R,S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, m.p. 159°-160° C; $[\alpha]_D^{25} -42.1^\circ$ ($c=0.63$, $CHCl_3$).

Proceeding as in Example 3, but replacing 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid with 5,6,7,8-tetrahydro-2-methoxy-1-naphthalenecarboxylic acid gave (R,S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-

2-methoxy-1-naphthalenecarboxamide, m.p. 270°-271° C.

Proceeding as in Example 1, but replacing 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid with 4-chloro-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid gave (R)-4-chloro-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with 4-amino-1-azabicyclo[2.2.2]octane gave N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with (R,S)-3-amino-1-azabicyclo[2.2.2]octane gave (R,S)-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with (R)-3-amino-1-azabicyclo[2.2.2]octane gave (R)-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-9-methyl-9-azabicyclo[3.3.1]nonane gave N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-8-methyl-8-azabicyclo[3.2.1]octane gave N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with exo-8-methyl-8-azabicyclo[3.2.1]octane gave N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3, but replacing (S)-3-amino-1-azabicyclo[2.2.2]octane with endo-1-azabicyclo[3.3.1]nonane gave N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

Proceeding as in Example 3 the following are prepared:

N-(exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; and

N-(exo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

EXAMPLE 4

N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

The following is the preparation of a compound of Formula II via Scheme I, Step 1 in which

n is 2;

each p, q, and n is 0; and

R¹ is

endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl.

A solution of 5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid (571 mg, 3.24 mmol), oxalyl chloride (0.44 mL, 3.0 mmol), and dimethylformamide (0.03 mL) in dichloromethane (20 mL) was stirred at room temperature for one hour. The mixture was then concentrated under reduced pressure and the residue was dissolved in toluene (10 mL). The resulting solution was added dropwise to a stirred mixture of endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane (300 mg, 3.24 mmol) and sodium carbonate (700 mg, 6.5 mmol) in water (5 mL) and toluene (25 mL). After 2 hours the mixture was

diluted with ethyl acetate (100 mL). The layers were separated and the organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford 700 mg of white crystals. A sample recrystallized from ethyl acetate gave *N*-(endo-9-methyl-8-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, m.p. 166°-167° C.

EXAMPLE 5

(*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide

The following is the preparation of a compound of Formula II via Scheme 1, Step 1 in which

n is 1;

p and q are 0; and

R^1 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (*RS*)-3-amino-1-azabicyclo[2.2.2]octane (1.00 g, 8 mmol) in toluene (20 mL) was added dropwise to a stirred solution of trimethylaluminum (8 mmol) in toluene (10 mL), so that the temperature did not exceed 10° C. The mixture was stirred for 30 minutes, and a solution of 2,6,7,8,9a-benzahydrocyclohept[*cd*]isobenzofuran-3-one (1.23 g, 6.6 mmol) in toluene (10 mL) was gradually added. The reaction mixture was heated under reflux 0.5 hours and then cooled to ambient temperature. Water was added gradually until a solid was precipitated, and the mixture was filtered. The solid was washed with ethyl acetate and the combined organic layer was evaporated to give (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 68% yield). Crystallization from ethanolic hydrochloric acid gave (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide hydrochloride, m.p. 239° C.

Reduction of (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 4.5 mmol) in ethanolic hydrochloric acid (20 mL) with 20% palladium hydride on carbon (0.5 g) was carried out at 50 psi for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. Purification of the product by column chromatography (10% methanol in methylene chloride and 1% ammonium hydroxide) gave (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide (0.32 g, 39% yield).

Proceeding as in Example 5 the following are prepared:

N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-9-methyl-8-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(exo-9-methyl-8-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; and

N-(exo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

EXAMPLE 6

(*RS*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one

The following is the preparation of a compound of Formula I via Scheme 1, Step 2 in which the optional bond is present;

n is 1;

each p , q and u is 0; and

R^1 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-iodanecarboxamide (2.07 g, 7.7 mmol), prepared as in Example 2, in dry tetrahydrofuran (100 mL) at -70° C. was treated with *n*-butyllithium (20 mmol). The reaction mixture was stirred at -10° C. for one hour, cooled to -70° C., and dimethylformamide (15 mmol) added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0° C. and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with 10N aqueous sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 1.75 g (81% yield) of white crystals. A sample recrystallized from ethyl acetate gave (*RS*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one, m.p. 146°-147° C. Anal.: Calcd. for $C_{19}H_{29}N_2O$: C, 77.11; H, 7.19; N, 9.99%. Found: C, 76.93; H, 7.23; N, 9.90%.

Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt monochloride adduct, m.p. 188°-190° C. Anal.: Calcd. for $C_{19}H_{29}N_2O \cdot HCl$: $C_{19}H_{29}NOH$: C, 66.19; H, 7.30; N, 7.72%. Found: C, 66.08; H, 7.35; N, 7.66%.

Proceeding as in Example 6, but replacing (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-iodanecarboxamide with (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-iodanecarboxamide, prepared as in Example 2, gave (*R*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one, m.p. 133.5°-136° C; $[\alpha]_D^{25} + 47.1^\circ$ ($c=0.41$, $CHCl_3$). Anal.: Calcd. for $C_{19}H_{29}N_2O$: C, 77.11; H, 7.19; N, 9.99%. Found: C, 77.49; H, 7.12; N, 9.84%, and (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one hydrochloride m.p. >285° C; $[\alpha]_D^{25} - 12.8^\circ$; Anal.: Calcd. for $C_{19}H_{29}N_2O \cdot HCl \cdot 0.5 H_2O$: C, 66.33; H, 6.81; N, 8.99%. Found: C, 65.94; H, 6.86; N, 8.33%.

Proceeding as in Example 6, but replacing (*RS*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-iodanecarboxamide with (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-iodanecarboxamide, prepared as in Example 2, gave (*R*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one and (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[*de*]isoquinolin-1-one hydrochloride.

EXAMPLE 7

(*R*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[*de*]isoquinolin-1-one

The following is the preparation of a compound of Formula I via Scheme 1, Step 2 in which the optional bond is present;

n is 2;

each p , q and u is 0; and

R^1 is 1-azabicyclo[2.2.2]oct-3-yl.

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A solution of *n*-butyllithium in hexane (80 mmol) was added dropwise at -70°C . to a solution of (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide (7.70 g, 21 mmol), prepared as in Example 3, in dry tetrahydrofuran (400 mL). The reaction mixture was stirred at -10°C . for one hour, cooled to -70°C ., and dimethylformamide (100 mmol) added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0°C . and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with concentrated ammonium hydroxide and extracted with ethyl acetate (100 mL). The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 7.98 g (93% yield) of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one as white crystals; m.p. $117-118^{\circ}\text{C}$; $[\alpha]_D^{25} + 41.2^{\circ}$ ($c=0.98$, CHCl_3).

Crystallization from ethanolic hydrochloric acid gave 9.75 g of the hydrochloride salt monohydrate adduct as white crystals; m.p. $>270^{\circ}\text{C}$. $[\alpha]_D^{25} - 8.4^{\circ}$ ($c=2.4$, H_2O). Anal: Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O} \cdot \text{HCl} \cdot \text{C}_2\text{H}_5\text{OH}$: C, 66.91; H, 7.73; N, 7.43%. Found: C, 66.77; H, 7.63; N, 7.27%.

Crystallization from isopropanolic hydrochloric acid gave the anhydrous hydrochloride salt.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $176-177^{\circ}\text{C}$.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $>275^{\circ}\text{C}$. $[\alpha]_D^{25} + 6.8^{\circ}$ ($c=2$, H_2O).

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenecarboxamide, prepared as in Example 3, gave (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-9-methoxy-1H-benz[de]isoquinoline-1-one.

Proceeding as in Example 7, but replacing (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-4-chloro-1-naphthalenecarboxamide, prepared as in Example 3, gave (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-7-chloro-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one.

EXAMPLE 8

2-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one

The following is the preparation of a compound of Formula I via Scheme 1, Step 2 in which the optional bond is present;

n is 2;

each p , q and u is 0; and

R^1 is endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl.

A solution of *n*-butyllithium in hexane (5 mmol) was added dropwise at -70°C . to a solution of N-(endo-9-

methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide (0.7 g, 2.34 mmol), prepared as in Example 4, in dry tetrahydrofuran (25 mL). The reaction mixture was stirred at -10°C . for one hour, cooled to -70°C ., and dimethylformamide (13 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0°C . and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with concentrated ammonium hydroxide and extracted with ethyl acetate (100 mL). The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to give 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one.

Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt monohydrate adduct; m.p. 216°C . Anal: Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O} \cdot \text{H}_2\text{O}$: C, 66.92; H, 7.73; N, 7.43%. Found: C, 66.43; H, 7.79; N, 7.33%.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with N-(1-azabicyclo[2.2.2]octan-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave 2-(1-azabicyclo[2.2.2]octan-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $335-337^{\circ}\text{C}$.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $269-270^{\circ}\text{C}$.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3, gave 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $>270^{\circ}\text{C}$.

Proceeding as in Example 8, but replacing N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide with N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, prepared as in Example 3 gave 2-(endo-1-azabicyclo[3.3.1]non-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride; m.p. $>360^{\circ}\text{C}$.

EXAMPLE 9

(RS)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one

The following is the preparation of a compound of Formula I via Scheme 1, Step 2 in which the optional bond is present;

n is 3;

each p , q and u is 0; and

R^1 is 1-azabicyclo[2.2.2]oct-3-yl.

A solution of *n*-butyllithium in hexane (2.7 mmol) was added dropwise at -70°C . to a solution of (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocycloheptene-1-carboxamide (0.37 g, 1.2 mmol), prepared as in Example 5, in dry tetrahydrofuran (10 mL). The reaction mixture was stirred at -10°C . for one

hour, cooled to -70°C , and dimethylformamide (1.5 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0°C and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with aqueous ammonium hydroxide. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated to give 0.15 g (40% yield) of (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one as a foam. Crystallization from ethanolic hydrochloric acid gave the hydrochloride salt, m.p. $>285^{\circ}\text{C}$.

Proceeding as in Example 9 the following are prepared: 2-(1-azabicyclo[2.2.2]oct-4-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; 2-(exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; 2-(endo-1-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one; and 2-(exo-1-azabicyclo[3.3.1]non-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one.

EXAMPLE 10

(R)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one

The following is the preparation of a diastereomeric mixture of a compound of Formula I via Scheme I, Step 3 in which

the optional bond is absent;

n is 2;

p , q and u are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydrobenz[de]isoquinoline-1-one (0.32 g, 1.1 mmol), prepared as in Example 3, in acetic acid (5 mL, containing 3 drops of 70% perchloric acid) was reduced with 20% palladium hydroxide on carbon (0.1 g) at 85°C and 50 psi for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in water (10 mL), basified with ammonium hydroxide solution, and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous potassium carbonate, filtered, and evaporated to give a diastereomeric mixture of (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one (0.18 g, 0.60 mmol) as a semi-solid. Crystallization from a mixture of ethanolic hydrochloric acid, isopropanol, and ether gave 0.8 g of the hydrochloride salt as white crystals; m.p. $>270^{\circ}\text{C}$. Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}\cdot\text{HCl}\cdot 0.25\text{H}_2\text{O}$: C, 67.64; H, 7.62; N, 8.30%. Found: C, 67.38; H, 7.70; N, 8.10%.

Proceeding as in Example 10 other compounds of Formula I wherein the optional bond is absent can be prepared.

EXAMPLE 11

2-(1-Azabicyclo[2.2.2]oct-3S-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one

The following is the preparation of a single diastereomer of Formula I in which

the optional bond is absent;

n is 2;

p , q and u are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

A diastereomeric mixture of 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one (16.1 g, 54.0 mmol), prepared as in Example 10, was dissolved in ethyl alcohol (100 mL) and hydrochloric acid (39.4 mmol) was added. Crystallization from ethanolic hydrochloric acid and ether gave a diastereomeric mixture of 70% 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one hydrochloride (A) and 30% 2-(1-azabicyclo[2.2.2]oct-3R-yl)-2,3,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one hydrochloride (B) (10.6 g, 35.6 mmol).

Recrystallization of the 70/30% mixture from ethyl alcohol (100 mL) gave a diastereomeric mixture of 94% A and 6% B (6.24 g, 20.9 mmol), $[\alpha]_D^{25} = -89.8^{\circ}$ ($c=0.1$, H_2O).

Recrystallization of the 94/6% mixture from ethyl alcohol gave a diastereomeric mixture of 98.9% A and 1.1% B (4.98 g, 15.4 mmol), m.p. 296°C – 297°C , $[\alpha]_D^{25} = -94.5^{\circ}$ ($c=0.53$, H_2O).

EXAMPLE 12

(S)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one N-oxide

The following is the preparation of a compound of Formula I via Scheme I, Step 3 in which the optional bond is present;

n is 2;

u is 1;

both p and q are 0; and

R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

m-Chloroperoxybenzoic acid (0.82 g, 4.7 mmol) was added in small portions at 0°C to a solution of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1-benz[de]isoquinoline-1-one, prepared as in Example 7, (1.16 g, 3.9 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for additional 0.5 hour at 0°C . The solvent was removed under reduced pressure. Purification of the residue by column chromatography (10% methanol in dichloromethane and 1% ammonium hydroxide) gave the N-oxide of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one (0.75 g; 62% yield) as an amorphous solid; m.p. 73°C – 75°C .

Proceeding as in Example 10, other compounds of Formula I wherein u is 1 are prepared.

EXAMPLE 13

The following are representative pharmaceutical formulations containing a compound of Formula I.

ORAL FORMULATION

A representative solution for oral administration contains:

Compound of Formula I	100-1000 mg
Chloro Acid Mann hydrous	100 mg
Sodium Hydroxide	10 mg
Flavoring	q.s.
Water	to 100 g

= 1 mg/mL

INTRAVENOUS FORMULATION

A representative solution for intravenous administration contains:

Compound of Formula I	10-100 mg
Dextrose Monohydrate	q.s. to make
Isotonic	
Chole Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.15 mg
Water for Injection	to 1.0 ml

TABLET FORMULATION

A representative tablet form of a compound of Formula I may contain:

Compound of Formula I	1%
Microcrystalline cellulose	75%
Starch Acid	25%
Colloidal Silicon	1%

EXAMPLE 14

5-HT₂ Receptor Binding Assay

The following describes an *in vitro* assay for determining the 5-HT₂ receptor binding affinity of compounds of Formula I. The method is essentially that described by Kilpatrick et al., previously cited, which measures the affinity for 5-HT₂ receptors of the rat cerebral cortex radiolabelled with [PH]quipazine.

Membranes are prepared from the cerebral cortices of rat brains homogenized in 50 mM Tris buffer (pH 7.4 at 4° C.) using a Polytron P10 tissue disrupter (setting 10, 2×10 sec bursts). The homogenate is centrifuged at 48,000×g for 12 min and the pellet obtained is washed, by resuspension and centrifugation, three times in homogenizing buffer. The three pellets are resuspended in the assay buffer, and are stored under liquid nitrogen until required.

The binding assays are conducted using a Tris-Krebs assay buffer of the following composition (mM): NaCl, 154; KCl, 5.4; KH₂PO₄, 1.2; CaCl₂·2H₂O, 2.5; MgCl₂, 1.0; glucose, 11; Tris, 10. Assays are conducted at 25° C. at 7.4 in a final volume of 0.25 ml. Zaccopride (1.0 mM) is used to define the non-specific binding (NSB). 5-HT₂ receptors present in rat cortical membranes are labelled using 0.3-0.7 nM [PH]quipazine (specific activity 50-66 Ci/mmol; New England Nuclear) in the presence of 0.1 mM paracetamol to prevent [PH]quipazine binding to 5-HT uptake sites. The rat cortex membranes are incubated with [PH]quipazine in the presence of 10 different concentrations of test compound ranging from 1×10⁻¹² to 1×10⁻⁴ molar. Incubations are conducted for 45 min at 25° C. and are terminated by vacuum filtration over Whatman GF/B glass fiber filter using a Brandel 48-well cell harvester. After filtration the filters are washed for 8 sec with 0.1M NaCl. The filters are pretreated with 0.3% polyethylenimine 18 hr prior to use in order to reduce filter binding of the radioligand. Radioactivity retained on the filters is determined by liquid scintillation counting.

The concentration of test compound producing 50% inhibition of radioligand binding is determined by an iterative curve fitting procedure. Affinities are expressed as the negative logarithm of the IC₅₀ value

(pIC₅₀). Compounds of Formula I exhibit 5-HT₂ receptor binding affinity, i.e., pIC₅₀ values greater than 6.

EXAMPLE 15

5-HT₂ Receptor Antagonist Assay (Von Bezold-Jarisch Reflex)

The following describes an *in vivo* method for determining the 5-HT₂ antagonist activity of compounds of Formula I. The method is a modified version of that described by Butler et al., Cohen et al., and Fogard, all previously cited, in which the 5-HT₂ selective agonist 2-methyl-5-hydroxytryptamine (2-m-5-HT) is substituted for 5-HT.

Male Sprague-Dawley rats, 250-350 grams, are anesthetized with urethane (1.4 g/kg, i.p.). A tracheostomy is performed and a tube is inserted into the trachea to facilitate respiration. Jugular and femoral veins are cannulated for intravenous administration of drug. The duodenum is cannulated for intraduodenal administration of drug. Heart rate is monitored by Gould ECG/Biotach amplifiers. After at least a 30 min equilibration period and prior to administration of test compound, control responses to intravenous administration of 2-m-5-HT are determined and a minimal dose producing sufficient and consistent bradycardia is chosen.

Potency

Intravenous challenges to 2-m-5-HT are administered every 12 minutes. Either vehicle or test compound is administered intravenously 5 minutes before each challenge to 2-m-5-HT. Each successive administration of test compound is increased in dosage until responses to 2-m-5-HT are blocked.

Duration

Vehicle or test compound is administered intravenously or intraduodenally and subsequent challenges to 2-m-5-HT are administered at 5, 15, 30, 60, 120, 180, 240, 300 and, in some instances, 360, 420 and 480 minutes post dose.

For both potency and duration studies heart rate (beats/min) is recorded continuously for the duration of the study. Responses to 2-m-5-HT are represented by the peak decrease in heart rate. Effects of test compounds are represented as percent inhibition of the bradycardia induced by 2-m-5-HT. Data are analyzed by a one-way repeated measures ANOVA and followed by pairwise comparison to vehicle control using Fisher's LSD strategy. From a dose-response curve so constructed, an ID₅₀ value is obtained to represent the dose that inhibited 50% of the bradycardia induced by 2-m-5-HT.

EXAMPLE 16

Ferret, Anti-Emetic Assay

The following describes the procedure for determining the intravenous (i.v.) effects of compounds of Formula I on cisplatin-induced emesis in ferrets.

Adult, male, castrated ferrets are allowed food and water *ad libitum* both prior to and throughout the testing period. Each animal is randomly chosen and anesthetized with a metofane/oxygen mixture, weighed and assigned to one of three test groups. While anesthetized an incision is made along the ventral cervical region approximately two to four centimeters in length. The jugular vein is then isolated and cannulated with a capped saline filled PE-50 polyethylene tubing. The

canula is exteriorized at the base of the skull and the incision closed with wound clips. The animals are then returned to their cages and allowed to recover from anesthesia prior to commencement of the study.

Vehicle or test compound is administered i.v. at 1.0 ml/kg and 1.0 mg/kg, respectively. Within 2.0 minutes of the administration of vehicle or test compound, cisplatin is injected i.v. at 1.0 mg/kg. The animals are then observed continuously for a 5 hour period and emetic responses (i.e., vomiting and/or retching) are recorded. For purposes of this example and that of Example 11, vomiting is defined as the successful evacuation of stomach contents and a single episode of retching is defined as rapid and successive efforts to vomit occurring within a one minute time period.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

Proceeding as in Example 8 but administering the test compounds by oral route, the anti-emetic effects of compounds of Formula I may be evaluated.

EXAMPLE 17

Dog, Anti-Emesis Assay

The following describes the procedure for determining the intravenous (i.v.) effects of compounds of Formula I on cisplatin-induced emesis in dogs.

Male and female dogs (6-15 kg) are fed one cup of dry dog food. One hour following feeding, cisplatin (cis-diamminedichloroplatinum) is administered i.v. at 3 mg/kg. Sixty minutes after the administration of cisplatin, either vehicle or test compound is injected i.v. at 0.1 ml/kg and 1.0 mg/kg, respectively. The dogs are then observed continuously for a 5 hour period and the emetic responses (i.e., vomiting and/or retching) are recorded.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

EXAMPLE 18

Prokinetic Assay

The following describes an in vivo method of determining the prokinetic activity of the compounds of Formula I by measuring the rate of gastric emptying of test meal in rats. The method is that described by Dropplman et al., previously cited.

Test meal is prepared by slowly adding 20 grams of cellulose gum (Hercules Inc., Wilmington, Del.) to 200 ml of cold distilled water that is being mixed in a Waring blender at approximately 20,000 rpm. Mixing continues until complete dispersion and hydration of the cellulose gum takes place (approximately 5 min). Three beef bouillon cubes are dissolved in 100 ml of warm water and then blended into the cellulose solution followed by 16 g of purified casein (Sigma Chemical Co.,

St. Louis, Mo.), 8 g of powdered confectioners sugar, 8 g of cornstarch, and 1 g of powdered charcoal. Each ingredient is added slowly and mixed thoroughly resulting in approximately 325 ml of a dark gray to black, homogeneous paste. The meal is then refrigerated overnight during which time trapped air escapes. Prior to the assay the meal is removed from the refrigerator and allowed to warm to room temperature.

Mature (170 to 204 g) male Sprague-Dawley rats are deprived of food for 24 hours with water ad libitum. On the morning of the study each animal is weighed and randomly assigned to treatment groups consisting of ten animals per group. Each rat receives either vehicle, test compound or the reference standard metoclopramide by intraperitoneal injection. At 0.5 hours post injection 3.0 ml of test meal is orally administered to each rat with a 5.0 ml disposable syringe. Five test meal samples are weighed on an analytical balance and these weights are averaged to find a mean test meal weight. At 1.5 hours post injection each rat is sacrificed by carbon dioxide asphyxiation and the stomach is removed by opening the abdomen and carefully clamping and cutting the esophagus just below the pyloric sphincter. Taking care not to lose any of the its contents, each stomach is placed on a small, pre-weighed and correspondingly labeled 7 ml weigh boat and immediately weighed on an analytical balance. Each stomach is then cut open along the lesser curvature, rinsed with tap water, gently blotted dry to remove excess moisture and weighed. The amount of test meal remaining in the stomach is represented by the difference between the weight of the full stomach and the weight of the stomach empty. The difference between the amount of test meal remaining and the mean test meal weight represents the quantity of test meal that empties during the 1.5 hour post injection period.

Responses are represented as grams of meal emptied or percent change from control. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined via Dunnett's t-test (Statistical Association Journal, December 1955, 1096-112).

EXAMPLE 19

Anxiolytic Behavior Assay

The following describes an in vivo method for determining anxiolytic activity of compounds of Formula I.

Naive male C57BL/6J mice, 18-20 g, are kept in groups of 10 mice in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

The automated apparatus for detecting changes in exploration is obtained from Omni-Tech Electronics Columbus Ohio and is similar to that of Crawley and Goodwin (1980), as described in Kilfoil et al., cited previously. Briefly, the chamber consists of a plexiglass box (44x21x21 cm), divided into two chambers by a black plexiglass partition. The partition dividing the two chambers contains a 13x5 cm opening through which the mouse can easily pass. The dark chamber has clear sides and a white floor. A fluorescent tube light (40 watt) placed above the chambers provides the only illumination. The Digiscan Animal Activity Monitor

System RXY2CM16 (Omnit-Tech Electronics) records the exploratory activity of the mice within the test chambers.

Prior to commencement of the study the mice are given 60 min to acclimatize to the laboratory environment. After a mouse receives an intraperitoneal (i.p.) injection of either test compound or vehicle it is returned to its home cage for a 15 min post-treatment period. The mouse is then placed in the center of the light chamber and monitored for 10 minutes.

Anxiolysis is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is reflected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increase in shuttle activity, increased or unaltered locomotor activity (number of grid lines crossed) and decreased time spent in the dark compartment.

EXAMPLE 20

Withdrawal Anxiety Assay

The following procedure describes a method to determine whether compounds of Formula I effect the anxiety that occurs after abruptly ceasing chronic treatment with drugs of abuse.

Naive male B6W mice (25-30 g) are caged in groups of ten in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

Levels of anxiety are determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 11). Anxiolysis is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is reflected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increased or unaltered locomotor activity (number of grid lines crossed), increased number of rears and decreased time spent in the dark compartment.

Increased exploratory activity in the lighted area is induced by treating the mice for 14 days with ethanol (10% w/v in drinking water), nicotine (0.1 mg/kg, i.p., twice daily), diazepam (10.0 mg/kg, i.p., twice daily) or cocaine (1.0 mg/kg, i.p., twice daily). Anxiolysis is assessed 1, 3, 7 and 14 days after commencement of the drug regime. The treatment is abruptly ceased and exploratory activity in the lighted area is determined 8, 24 and 48 hours thereafter. Vehicle or test compounds are administered during the withdrawal phase by intraperitoneal injection. Responses are represented as inhibition of the decrease in anxiolytic behavior after the ethanol, cocaine, diazepam or nicotine treatment is ceased.

EXAMPLE 21

Cognitive Enhancement Assay

The following describes a model to determine the cognitive enhancing effects of compounds of Formula I.

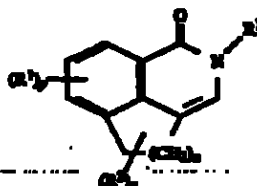
Young adult and aged B6W mice are caged in groups of ten in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

Levels of anxiety are determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 11). Mice are exposed to the two-com-

partment test area over a 3 day period. The young mice habituate to the test area by day 3 and spend less time exploring the lighted area, whereas exploratory activity in the lighted area remains constant through day 3 for the aged mice. Exploratory activity is seen as latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), locomotor activity (number of grid lines crossed), number of rears and time spent in the lighted compartment. Vehicle or test compounds are administered to the aged mice by intraperitoneal injection. Cognitive enhancing effects in the aged rats are reflected by a decrease in exploratory activity by day 3.

We claim:

1. A compound of Formula I



in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

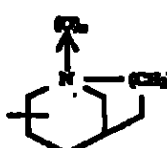
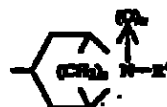
p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each R¹ is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

each R² is lower alkyl; and

R³ is a group selected from Formulas (a), (b), (c) and (d):



in which
r is 0 or 1;

z is 1, 2 or 3; and
 R⁴ is C₁₋₃ alkyl, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyl-C₁₋₄ alkyl, or a group (CH₂)_tR⁵ where t is 1 or 2 and R⁵ is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkyl, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C₁₋₄ alkyl optionally substituted by hydroxy, C₁₋₄ alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acylary; the pharmaceutically acceptable salts, individual isomers, or mixtures of isomers thereof.

2. A compound of claim 1 in which both q and u are 0, p is 0, 1 or 2, each R' is independently selected from halogen, lower alkoxy or amino and R² is lower alkyl.

3. A compound of claim 2 in which p is 0, and R² is methyl.

4. A compound of claim 3 in which R³ is one of the following groups:
 1-azabicyclo[2.2.2]oct-3-yl;
 1-azabicyclo[2.2.2]oct-4-yl;
 endo-8-methyl-8-azabicyclo[3.3.1]non-3-yl;
 endo-8-methyl-8-azabicyclo[3.3.1]non-3-yl;
 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
 endo-1-azabicyclo[3.3.1]non-4-yl; or
 endo-1-azabicyclo[3.3.1]non-4-yl.

5. A compound of claim 4 in which the optional bond is present.

6. A compound of claim 5 in which z is 1.

7. A compound of claim 6 in which R³ is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

8. A compound of claim 7 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

9. A compound of claim 8 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one hydrochloride.

10. A compound of claim 6 in which R³ is 8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely, 2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinoline-1-one hydrochloride.

13. A compound of claim 5 in which z is 2.

14. A compound of claim 13 in which R³ is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

15. A compound of claim 14 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

16. A compound of claim 15 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one hydrochloride.

17. A compound of claim 14 which is (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

18. A compound of claim 17 which is (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or hydrochloride.

19. A compound of claim 13 in which R³ is 1-azabicyclo[2.2.2]oct-4-yl, namely 2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

20. A compound of claim 13 in which R³ is endo-8-methyl-8-azabicyclo[3.3.1]non-3-yl, namely 2-(endo-8-methyl-8-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one.

21. A compound of claim 13 in which R³ is 8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

22. A compound of claim 21 which is 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

23. A compound of claim 21 which is 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

24. A compound of claim 13 in which R³ is endo-1-azabicyclo[3.3.1]non-4-yl, namely 2-(endo-1-azabicyclo[3.3.1]non-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

25. A compound of claim 5 in which z is 1.

26. The compound of claim 25 in which R³ is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

27. A compound of claim 4 in which the optional bond is absent.

28. A compound of claim 27 in which z is 1.

29. A compound of claim 27 in which z is 2.

30. A compound of claim 29 in which R³ is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one.

31. A compound of claim 30 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

32. A compound of claim 31 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one hydrochloride.

33. A compound of claim 30 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one or a pharmaceutically acceptable salt thereof.

34. A compound of claim 33 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one hydrochloride.

35. A compound of claim 30 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one a pharmaceutically acceptable salt thereof.

36. A compound of claim 35 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one hydrochloride.

37. A compound of claim 36 which is 2-(1-azabicyclo[2.2.2]oct-3R-yf)-2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

38. A compound of claim 37 which is 2-(1-azabicyclo[2.2.2]oct-3R-yf)-2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one hydrochloride.

39. A compound of claim 27 in which x is 1.

40. A pharmaceutical composition for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain, which composition comprises a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

41. A method for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain in an animal in need of such treatment; which method comprises administering a therapeutically effective amount of a compound of claim 1 to such animal.

42. A method of claim 41 in which the condition is a gastrointestinal disorder treatable with prokinetic agents.

43. A method of claim 41 in which the condition is pain.

44. A method of claim 41 in which the condition is anxiety/depressive state.

45. A method of claim 44 in which the condition is the side effects caused by withdrawal from an addictive substance.

46. A method of claim 41 in which the condition is emesis.

47. A method of claim 46 in which the condition is emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, or recovering from surgical anesthesia or undergoing drug therapy in general in which a significant side effect is emesis.

48. A method of claim 47 in which the compound is (S)-2-(1-azabicyclo[2.2.2]oct-3-yf)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

49. A method of claim 47 in which the compound is 2-(3S-1-azabicyclo[2.2.2]oct-3-yf)-2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

50. A method of claim 42 in which the compound is (S)-2-(1-azabicyclo[2.2.2]oct-3-yf)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one.

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The Efficacy of RS-25259, a Long-Acting Selective 5-HT₃ Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures

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We evaluated the safety and efficacy of RS-25259, a potent and long-acting selective 5-HT₃ receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) in women undergoing hysterectomy procedures. In this randomized, double-blind, placebo-controlled, dose-ranging study, 218 healthy, consenting women were assigned to one of the six treatment groups: placebo or RS-25259 0.1, 0.3, 1.0, 3.0, or 30 µg/kg. All patients underwent a standardized general anesthetic technique. The study medication was administered IV 20–30 min before the end of surgery. During the initial 24-h period after surgery, the incidence of vomiting, the need for rescue antiemetics, the time to the first episode of emesis, and administration of rescue antiemetic medication, as well as a nausea visual analog scale and verbal categorical scale scores were recorded. In addition, recovery times from the end of anesthesia and the incidences of perioperative side effects were noted. Only 30 µg/kg RS-25259 significantly decreased the incidence of vomiting and the

requirement for rescue antiemetics. The largest dose of RS-25259 also delayed the time to the first emetic episode and reduced the number of treatment failures. However, no differences were found in the severity of postoperative nausea (versus saline), and postoperative headaches were more common after the administration of RS-25259 0.3–30 µg/kg IV. In conclusion, RS-25259 30 µg/kg IV was effective in reducing the incidence of PONV after major gynecologic surgery, but the occurrence of headaches with the larger doses of RS-25259 is a concern. Implications: RS-25259, a long-acting 5-HT₃ antagonist, was effective in reducing postoperative vomiting only at the largest dose studied (30 µg/kg). However, RS-25259 had no anti-nausea activity, and the larger doses were associated with an increased incidence of headaches in the postoperative period.

(Anesth Analg 1998;87:462–7)

Nausea, retching, and vomiting are common complications after major gynecologic surgery (1–3). Dehydration, electrolyte imbalance, excessive tension on suture lines, venous hypertension, and increased hematoma formation are secondary problems related to persistent or intractable postoperative emesis (4). Several different classes of prophylactic antiemetics have been administered in an attempt to decrease the incidence of postoperative nausea and vomiting (PONV). However, many of the commonly

used antiemetics are associated with undesirable side effects (5,6).

Ondansetron, the first 5-HT₃ receptor antagonist, possesses antiemetic activity in women who develop intractable PONV after gynecologic surgery (7). Studies have confirmed the efficacy of ondansetron in both the treatment and prevention of PONV (8,9). However, a meta-analysis suggested that the use of ondansetron is associated with an increased incidence of headaches and transient elevations in liver enzymes (10).

RS-25259 is a potent and highly selective 5-HT₃ receptor antagonist (11) that is more effective than ondansetron in preventing chemotherapy-induced emesis in animals (12). In this preliminary, double-blind, dose-ranging study, the efficacy and safety of RS-25259 were evaluated when administered prophylactically to women undergoing major gynecologic surgical procedures.

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Methods

This randomized, double-blind, placebo-controlled study was performed at two medical centers (University of Texas Southwestern Medical Center in Dallas, TX and Wake Forest University Baptist Medical Center in Winston-Salem, NC). After obtaining institutional review board approval at both medical centers, 218 ASA physical status I or II consenting women undergoing an abdominal or vaginal hysterectomy with a standardized general anesthetic technique were enrolled in the study. Exclusion criteria included pregnancy, body weight >100% of the calculated ideal body weight, hypersensitivity to 5-HT₃ antagonists, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before the operation, a recent history of narcotic or alcohol abuse, and preexisting abnormalities involving the renal, hepatic, cardiovascular, metabolic, or endocrine systems. Patients were asked to provide a detailed medical history and demographic information (including age, weight, height, alcohol or drug consumption, last menstrual period, any history of PONV or motion sickness).

Because a history of PONV is associated with an increased risk of PONV after a subsequent operation (1), patients were assigned to one of two strata based on their history of PONV after general anesthesia. Within each strata, patients were randomized to one of six prophylactic treatment groups: placebo (saline) or 0.1, 0.3, 1.0, 3.0, or 30 µg/kg RS-25259. Each dose of study medication was prepared by the hospital pharmacy in a total volume of 15 mL of isotonic sodium chloride solution and was administered IV over 30 s approximately 20–30 min before the end of surgery.

In the preoperative holding area, patients completed a baseline 100-mm visual analog scale (VAS) for nausea (0 = no nausea to 100 = maximal nausea) and a verbal categorical scale (VCS) (1 = no nausea, 2 = mild nausea, 3 = moderate nausea, or 4 = severe nausea). Midazolam 2 mg IV was used to premedicate all patients. On arrival in the operating room, routine monitoring devices consisting of a noninvasive blood pressure cuff, pulse oximeter probe, and electrocardiogram were placed. General anesthesia was induced with thiopental and an opioid analgesic (either fentanyl or sufentanil) and was maintained with isoflurane, nitrous oxide (N₂O) in oxygen, and a nondepolarizing neuromuscular blocking drug. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. After tracheal extubation, the patients were transported to the postanesthesia care unit (PACU) where morphine or meperidine was administered as needed for postoperative analgesia.

The anesthetic time (from induction of anesthesia to discontinuation of N₂O) and the operating time (from surgical incision to completion of the last suture) were

recorded. The times at which patients were able to follow commands (e.g., squeeze the investigator's hand) and were discharged from the PACU were also noted. Episodes of PONV and administration of rescue antiemetics were recorded during the first 24-h period after surgery. An emetic episode was defined as a single vomiting or retching event or any combination of these events separated by less than 1 min.

Rescue antiemetic medication was administered after a repeat emetic episode or at the request of the patient. In addition, the time interval to first experiencing an emetic episode or to receiving a rescue antiemetic, as well as treatment failures (defined as a situation in which the patient experienced a single emetic episode or required rescue antiemetic medication), were noted. On arrival in the PACU and 1, 2, 4, 8, 12, 16, 20, and 24 h after the end of anesthesia patients were asked to assess their degree of nausea using the VAS and VCS. At the end of the 24-h observation period, a VCS was also used to evaluate the overall degree of nausea during the postoperative period. Overall patient satisfaction with the control of their PONV was assessed using a VCS (1 = very good, 2 = good, 3 = fair, and 4 = poor). Finally, all patients were contacted 24 h, 3 days, and 14 days after the operation and asked the nonspecific question, "Is anything bothering you?"

The statistical analysis consisted of a one-way analysis of variance (ANOVA) to compare the continuous variables among the six treatment groups. If a significant difference was noted, Scheffé's multiple comparison test was performed to determine intergroup differences. A two-way ANOVA was used to analyze the repeated measures. Categorical variables were analyzed by using the χ^2 test or Fisher's exact test as appropriate. All tests were two-sided, and a *P* value <0.05 was considered statistically significant. Data are presented as mean values $\pm$ SD, numbers, or percentages.

Results

The demographic data for the six treatment groups are summarized in Table 1. The six groups were comparable with respect to age, weight, height, number of days since the start of their last menstrual cycle, percentage of patients with a history of PONV and motion sickness, and type of hysterectomy procedure (i.e., transabdominal versus vaginal). The dosages of anesthetic and analgesic drugs administered during the intraoperative and postoperative period, the duration of anesthesia and surgery, and the time to following verbal commands, and the duration of the PACU stay were also similar among all six groups.

Within the first 2 h after surgery, the incidence of vomiting was significantly reduced in patients receiving RS-25259 30 µg/kg IV compared with the group

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Table 1. Demographic Characteristics and Surgical and Recovery Times

	Saline	RS-25259 (µg/kg)				
		0.1	0.3	1.0	3.0	30
n	36	27	41	35	40	39
Age (yr)	41 ± 8	43 ± 9	39 ± 7	39 ± 9	42 ± 8	42 ± 8
Weight (kg)	70 ± 14	76 ± 18	70 ± 16	74 ± 17	73 ± 14	71 ± 13
Height (cm)	162 ± 10	164 ± 7	163 ± 7	164 ± 9	164 ± 7	162 ± 7
Last menstrual period						
0-8 d	7	7	12	12	10	11
9-16 d	4	5	6	5	8	8
>16 d	24	14	23	16	21	20
Unknown	1	1	0	2	1	0
Previous PONV	14	12	14	13	15	12
Previous motion sickness	5	4	3	6	5	2
Intraoperative opioid analgesics (µg)						
Fentanyl	271 ± 140	304 ± 129	308 ± 92	262 ± 94	242 ± 103	277 ± 113
Sufentanil	89 ± 30	88 ± 27	86 ± 29	78 ± 27	92 ± 33	86 ± 32
Postoperative opioid analgesics (mg)						
Morphine	47 ± 35	56 ± 31	46 ± 21	59 ± 25	60 ± 31	56 ± 26
Meperidine	283 ± 173	273 ± 102	243 ± 151	221 ± 180	217 ± 152	334 ± 118
Anesthetic time (min)	132 ± 46	147 ± 73	148 ± 64	146 ± 76	138 ± 57	148 ± 71
Operative time (min)	108 ± 39	121 ± 61	122 ± 57	122 ± 72	117 ± 53	120 ± 66
Respond to commands (min)	10 ± 7	11 ± 6	11 ± 11	12 ± 10	11 ± 6	9 ± 6
Duration of PACU stay (min)	102 ± 34	101 ± 30	102 ± 33	101 ± 40	106 ± 33	87 ± 38

Values are means ± sd or h.
PONV = postoperative nausea and vomiting; PACU = postanesthetic care unit.

receiving saline or RS-25259 0.1 or 1.0 µg/kg IV (Table 2). Similarly, RS-25259 30 µg/kg IV was significantly more effective in preventing vomiting within the first 12 h after surgery than either the saline or RS-25259 0.1 µg/kg IV. RS-25259 30 µg/kg IV also marginally decreased the number of emetic episodes within the first 24 h postoperatively compared with placebo treatment ($P = 0.05$). Although the need for rescue antiemetics within the first 2 h was similar among all groups, RS-25259 1.0, 3.0, and 30 µg/kg IV significantly decreased the antiemetic requirement compared with saline within the first 12 h after surgery. Within the first 24 h after surgery, only the 30 µg/kg IV dose of RS-25259 significantly reduced the antiemetic requirement compared with the saline group. In addition, the time to the first emetic episode was significantly shorter in patients receiving saline or RS-25259 0.1 µg/kg IV compared with those receiving 30 µg/kg IV RS-25259. Similarly, the mean time to the first episode of vomiting was significantly shorter in the patients receiving RS-25259 0.1 µg/kg IV than in those receiving RS-25259 0.3 µg/kg IV. The percentage of treatment failures was significantly higher in the saline group than in the RS-25259 30 µg/kg IV group during the first 24 h after surgery (Table 2).

Among patients with a history of PONV, there were no differences in the incidence of vomiting or in the

need for rescue antiemetic medication among the six groups (Table 3). However, among patients with no history of PONV, RS-25259 30 µg/kg IV was significantly more effective in the prevention of emetic episodes within the first 2, 12, and 24 h after surgery, and it decreased the need for rescue antiemetic therapy within 12 and 24 h after surgery compared with saline. RS-25259 1.0 µg/kg IV was also effective in reducing the number of emetic episodes and the need for antiemetic rescue medication within 12 h compared with saline (Table 4). Of interest, the VAS and VCS scores for nausea did not differ among the six groups (data not shown). The overall satisfaction with the control of PONV in the first 24 h after surgery was also similar (data not presented).

Finally, the overall incidences of adverse side effects were similar among all treatment groups (Table 5). However, more postoperative headaches were noted in patients who received larger doses of RS-25259 (0.3-30 µg/kg) compared with those who received saline and the smallest dose of RS-25259 (0.1 µg/kg) ($P < 0.02$).

Discussion

This clinical study demonstrated that the IV administration of RS-25259 30 µg/kg 20-30 min before the

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Table 2. Patients Experiencing Vomiting, Receiving Antiemetic (Rescue) Medication, and Reported as Treatment Failures in the First 24 Hours After Surgery

	Saline	RS-25259 (µg/kg)				
		0.1	0.3	1.0	3.0	30
n	36	27	41	35	40	39
Vomiting (%)						
0-2 h	17	15*	10	14	13	0†‡
0-12 h	39	41	24	23	23	13*†
0-24 h	47	44	32	34	30	26
Rescue antiemetics (%)						
0-2 h	31	22	22	23	20	23
0-12 h	72	63	56	43*	43*	46*
0-24 h	75	67	61	54	53	49*
Time to first emesis (min)	339 ± 319	213 ± 189	637 ± 530†	428 ± 507	475 ± 544	795 ± 416*†
Time to rescue antiemetic (min)	234 ± 211	314 ± 308	326 ± 264	381 ± 447	490 ± 473	474 ± 330*
Treatment failures (%)	78	70	63	60	58	51*

Values are percentages or means ± sd.
* P < 0.05 versus saline.
† P < 0.05 versus RS-25259 0.1 µg/kg.
‡ P < 0.05 versus RS-25259 1.0 µg/kg.

Table 3. Patients with a History of PONV Who Experienced Vomiting or Required Rescue Antiemetic Therapy Within 24 Hours After Surgery

	Saline	RS-25259 (µg/kg)				
		0.1	0.3	1.0	3.0	30
n	14	12	14	13	15	12
Vomiting (%)						
2 h	14	25	14	31	20	0
12 h	36	50	43	46	27	25
24 h	43	58	50	54	33	42
Rescue antiemetics (%)						
2 h	29	33	29	46	20	33
12 h	79	75	79	62	47	67
24 h	79	75	86	62	67	67

PONV = postoperative nausea and vomiting.

Table 4. Patients with No History of PONV Who Experienced Emesis or Required Rescue Antiemetics Within 24 Hours After Surgery

	Saline	RS-25259 (µg/kg)				
		0.1	0.3	1.0	3.0	30
n	22	15	27	22	25	27
Vomiting (%)						
2 h	18	7	7	5	8	0*
12 h	41	33	15	9*	20	7*
24 h	50	33	22	23	28	19*
Rescue antiemetics (%)						
2 h	32	13	19	6	20	19
12 h	68	53	44	32*	40	37*
24 h	73	60	48	50	44	41*

PONV = postoperative nausea and vomiting.
* P < 0.05 versus saline.

end of surgery was effective in decreasing emesis in women undergoing major gynecologic surgery. However, analogous to the recent findings of Tramer et al. (10) with ondansetron, larger doses of RS-25259 were associated with more headaches. Although the length of stay in the PACU was slightly shorter in the large-dose RS-25259 group, this difference was not statistically significant. Moreover, the patients' overall satisfaction with the control of the PONV symptoms was not improved by the administration of RS-25259. Considering the more meaningful outcome measures (e.g., recovery times, patient satisfaction), RS-25259 seems to be of limited benefit in this high-risk patient population.

The 5-HT₃ receptor antagonists are effective in reducing emesis by acting on both the central and peripheral nervous systems (13). Ondansetron has been successfully used for both prophylaxis and treatment of PONV with few clinically significant adverse effects

(7-9). Although apparently free of activity at histaminergic, dopaminergic, or cholinergic receptors (14), side effects such as chest pain, headaches, and extrapyramidal symptoms have been reported with ondansetron (15,16) and other 5-HT₃ antagonists. Granisetron and tropisetron, two more recently introduced 5-HT₃ receptor antagonists that have also been reported to decrease emesis after surgical procedures (17,18), possess longer elimination half-life values than ondansetron [9-11 h (19) and 6-7 h (20) versus 2.8 ± 0.6 h (21), respectively]. However, the long-lasting antiemetic activity associated with granisetron is allegedly due to its high affinity for the 5-HT₃ receptor (22,23). Of interest, Naguib et al. (24) reported that the prophylactic administration of ondansetron was as effective as granisetron and tropisetron in reducing the incidence of PONV during the first 24 h after laparoscopic cholecystectomy. Unfortunately, none of the currently

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Table 5. Perioperative Side Effects

	Saline	RS-25259 ($\mu\text{g/kg}$)					
		0.1	0.3	1.0	3.0	30	
n	36	27	41	35	40	39	
Side effects (%)							
Pain	14	7	15	9	13	10	
Anxiety	0	4	5	0	5	5	
Constipation	39	37	32	31	33	23	
Dizziness	0	4	5	3	5	8	
Drowsiness	3	4	5	3	0	0	
Headache	6	7	17*	23*	15*	21*	
Insomnia	11	19	7	14	18	8	
Itching	8	22	17	14	15	8	
Rash	6	7	5	6	3	0	

* $P < 0.05$ versus saline and RS-25259 0.1 $\mu\text{g/kg}$.

available 5-HT₃ receptor antagonists are completely effective in preventing PONV.

RS-25259 is a highly potent and selective 5-HT₃ receptor antagonist (11) that decreases chemotherapy-induced emesis (12). The dose range chosen for this preliminary study was based on the single-dose safety and tolerability studies performed in healthy male volunteers (Robert Smith, PhD, personal communication, 1993). After IV doses of 0.3–90 $\mu\text{g/kg}$, RS-25259 has an elimination half-life of 30–40 h in humans (data on file at Syntex/Roche, Palo Alto, CA). For this preliminary dose-ranging study, a female surgical population undergoing major gynecologic procedures was chosen because it is at high-risk of developing PONV. These results suggest that smaller doses of RS-25259 are ineffective in preventing of PONV. Only the largest dose of RS-25259, 30 $\mu\text{g/kg}$ IV, was effective in decreasing vomiting and the need for rescue antiemetic drugs during the first 24 h after major gynecologic surgical procedures. Unfortunately, even the largest dose of RS-25259 did not reduce the severity of nausea during the early postoperative period. Like other 5-HT₃ receptor antagonists (17,25), RS-25259 also seems to increase postoperative headaches. Although oral RS-25259 1 $\mu\text{g/kg}$ is effective in preventing PONV in outpatients undergoing laparoscopic surgery (26), it was less effective in this inpatient population undergoing major gynecologic procedures.

When patients were stratified according to their history of PONV, RS-25259 was ineffective in the prevention of PONV in the high-risk subpopulation. It is possible that the failure to demonstrate a beneficial effect in patients with a history of PONV was related to the small number of subjects in these subgroups. The lack of an active comparative drug also limits the clinical implications of this study. However, before initiating comparative clinical trials with a new antiemetic drug, it is necessary to determine the effective

dose range and the side effect profile using a placebo-controlled, dose-ranging study design.

In conclusion, RS-25259 30 $\mu\text{g/kg}$ IV was effective in preventing PONV in women undergoing major gynecologic surgery. However, it did not decrease postoperative nausea or improve patient satisfaction. Of concern, postoperative headaches were increased in patients who received larger doses of RS-25259.

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Palonosetron, a selective 5-HT₃ receptor antagonist, is being developed by Helsinn for the potential treatment of chemotherapy-induced nausea and vomiting. By 1999, it was in phase III trials [361633], and as of May 2002, an NDA filing was scheduled for the third quarter of 2002 [450577].

Introduction

Palonosetron is a 5-HT₃ receptor antagonist that was previously under development by Syntex (now Roche Bioscience) and is presently being developed by Helsinn Healthcare SA. There is only scarce information on the agent and a number of studies have been published in abstract form only. Double-blind, randomized phase III trials are under way in the US and Western Europe, aimed at evaluating the suitability of palonosetron as a potential treatment for chemotherapy-induced nausea and vomiting. These trials will enroll over 1800 cancer patients receiving highly or moderately emetogenic chemotherapy [424144] and include a study in children [361563]. In April 2002, a preliminary analysis of the pivotal phase III trials demonstrated that palonosetron met the primary efficacy endpoint of a 24 h complete response. In addition, the complete response rate for the 24 to 120 h time period favored palonosetron over the comparator agents, i.e. currently marketed 5-HT₃ receptor antagonists [448290]. The submission of a New Drug Application for palonosetron in the US was planned to take place in the third quarter of 2002 [450577].

Synthesis and SAR

Palonosetron was developed as one of the conformationally restricted analogs of the potent 5-HT₃ receptor antagonists tropisetron and granisetron [161399]. Of these analogs, palonosetron proved to be the highest affinity 5-HT₃ receptor ligand and the most potent 5-HT₃ receptor antagonist *in vivo*, and to be potent in blocking cisplatin-induced emesis in both the ferret and the dog [161399]. The dissociation of [³H]palonosetron as well as of other antagonists, but not of [³H]granisetron, from both cloned and native 5-HT₃ receptors was revealed to be markedly delayed in the presence of 5-HT or 2-methyl-5-HT. This suggests that agonists can modify the interaction of palonosetron and other, but not all, antagonists at the 5-HT₃ receptor [209700]. Palonosetron does not exist as a racemic mixture as do other 5-HT₃ antagonists, but rather as a single stereoisomer. A short and efficient total synthesis has been described [361695].

Pharmacology

Palonosetron was shown to be a potent and selective 5-HT₃ receptor antagonist in a series of *in vitro* studies [173464]. At

Originator Roche Bioscience

Licenseses Helsinn Healthcare SA, MGI Pharma Inc

Status Phase III Clinical

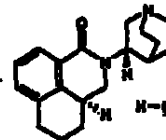
Indication Emesis

Action 5-HT₃ antagonist, Anti-emetic

Synonyms & Analogs RS-25233-197, RS-25233-198, RS-25259-007, RS-25259-197, RS-25259-198, RS-42358, RS-42358-197, RS-42358-198

CAS 1H-Benz[de]isoquinolin-1-one, 2-(3S)-(1-azabicyclo[2.2.2]oct-5-yl-2,3,3a,4,5,6-hexahydro-, monohydrochloride

Registry Nos: 135729-61-2, 135729-62-3



5-HT₃ receptors mediating the contractile responses of the guinea pig isolated ileum to 5-HT, the affinity for 5-HT₃ receptors of the four enantiomers, palonosetron (S,S), RS-25259-198 (R,R), RS-25233-197 (S,R) and RS-25233-198 (R,S), was tested. Palonosetron had the highest affinity for 5-HT₃ receptors, the rank order of pK_i values being (S,S) > (R,S) > (S,R) = (R,R). Palonosetron, but not the other enantiomers, unambiguously antagonized contractile responses to 5-HT. The affinities of the four enantiomers at 5-HT₃ receptors in membranes from NG-108-15 cells, as evaluated by a [³H]quipazine binding assay, revealed a similar rank order. In membranes from NG-108-15 cells, in the rat cerebral cortex and in the ileal myenteric plexus of the rabbit and guinea pig, palonosetron displaced binding of a radiolabeled structural analog, the selective 5-HT₃ receptor ligand [³H]RS-42358-197, but exhibited low affinity at 28 other receptors including adrenoceptors, muscarinic (M₁, M₂, M₃, M₄), dopamine (D₁, D₂), opiate, as well as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2B} receptors [173464]. In saturation binding studies using membranes from NG-108-15 cells and human kidney 293E1 cells transfected with a cloned homomeric α subunit of a murine 5-HT₃ receptor, [³H]palonosetron exhibited a 3- to 4-fold higher affinity than [³H]RS-42358-197, although the same density of sites was labeled. Competition studies with [³H]palonosetron in NG-108-15 cells indicated a pharmacological specificity of palonosetron entirely consistent with labeling a 5-HT₃ receptor: the rank order of affinity of 5-HT₃ receptor antagonists displacing [³H]palonosetron was palonosetron > (S)-zacopride > granisetron > tropisetron > (R)-zacopride > ondansetron > MDL-72222. In contrast to the majority of radioligands available to label 5-HT₃ receptors, [³H]palonosetron also

A randomized, double-blind study assessed the pharmacokinetic profile of single doses of palonosetron (0.3, 3, 10, 30 and 90 µg/kg) in 37 chemotherapy-naïve patients with histologically proven cancer who were scheduled to receive chemotherapy [452078]. Palonosetron was administered 30 min prior to an initial dose of cisplatin (> 70 mg/m²) or cyclophosphamide (> 1100 mg/m²). Eleven blood samples were drawn during the first 24 h and at 48, 72, 120 and 168 h

after injection, and analyzed using a validated plasma assay sensitive to 0.020 ng/ml. The area under the curve of plasma concentrations increased dose-proportionally. The time to the maximal plasma concentrations ranged from 8.6 to 49.6 min post dose, the maximal plasma concentrations from 0.880 to 336 ng/ml, the elimination half-life from 43.7 to 128 h (ie, significantly longer than the elimination half-lives of other 5-HT₁ receptor antagonists), the clearance from 1.51 to 2.23 ml/min/kg, and the volume of distribution from 6.83 to 12.5 l/kg. The kinetics were dose-proportional, with no statistically significant differences across the dose levels [452078].

Phase III

The results of a multi-center, randomized, double-blind, phase III trial were presented at the 14th International Symposium of the Multinational Association of Supportive Care in Cancer, which took place in Boston, MA, USA. In this trial, 369 patients received doses of either palonosetron (0.25 or 0.75 mg iv) or dolasetron (100 mg) 30 min prior to the administration of a moderately emetogenic chemotherapy regimen. The 1-day complete response rate, ie, the percentage of patients who did not experience vomiting and did not need any rescue medication within the first 24 h, was slightly higher after both palonosetron dosages than after dolasetron, and thus met the primary endpoint of non-inferiority. The delayed period complete response rate (the percentage of patients who did not experience vomiting and did not need any rescue medication within the 24 to 120 h period) for both doses of palonosetron (54 and 56.6% for the lower and higher doses, respectively) was significantly superior to dolasetron (38.7%). The side effects reported most frequently, mild constipation and headache, were mild and similar across all treatments [456276], [458872].

Side Effects and Contraindications

In dose-ranging studies carried out in postoperative patients, more headaches were reported by individuals who had received higher doses of palonosetron than by those who had received a low dose of the agent [454632] or placebo [454628], [454632]. 173 individuals evaluated for safety had complained, after palonosetron administration, of

headache and constipation at rates 6 and 11% higher than the incidence rate with placebo; both side effects were 'generally mild-to-moderate' [454635]. No other adverse effects had been observed to occur more frequently after palonosetron than after placebo [410609], [454635]. In a dose-ranging study carried out in cancer patients scheduled for chemotherapy, individuals who received one of five doses of palonosetron 30 min prior to an initial dose of cisplatin or cyclophosphamide, reported non-specified and non-dose-dependent adverse events of a generally mild-to-moderate nature, with the incidence and intensity of such events being equally distributed among dose levels [452078]. The available data suggest that palonosetron's side effect profile does not differ from the side effect profile of currently available 5-HT₁ receptor antagonists.

Current Opinion

Information on the effects of palonosetron is scarce. In the two large phase II studies carried out in patients undergoing laparoscopic surgery [454628] and vaginal hysterectomy [454632], palonosetron administered both po [454628] and iv [454632] prevented postoperative vomiting significantly more often than did placebo. However, the superiority of the most effective doses of palonosetron over placebo was modest, the NNT amounting to 3.8 [454628] and 4.8 [454632], respectively. Palonosetron's effect on nausea appears less consistent as the severity of nausea remained unaffected in one of the trials reported [454632]. The extended elimination half-life of palonosetron [410609], [452078], [454635] may result in a longer duration of action than the one observed after treatment with currently available 5-HT₁ antagonists. Apart from headache and constipation, effects that are also observed after the administration of marketed 5-HT₁ receptor antagonists, no side effects were reported to have occurred more frequently after palonosetron than after placebo administration.

Commercial Opinion

In June 2002, US Bancorp Piper Jaffrey expected that an NDA for palonosetron would be filed in the third quarter of 2002. Estimate of sales was US \$19 million in 2003, US \$60 million in 2004 and US \$139 million in 2005 [458872].

Licensing

Helalinn Healthcare SA

By April 2001, Helalinn had started phase III trials with palonosetron, but has not disclosed any licensing details [361563].

MGI Pharma Inc

In February 2001, MGI Pharma signed a letter of intent for exclusive North American license and distribution rights to palonosetron. Under the terms of the letter, MGI Pharma made a US \$5 million deposit to Helalinn. MGI Pharma was also to make additional payments upon concluding the license agreement and based on the achievement of certain milestones leading up to the approval of palonosetron in the US. Helalinn was to continue to fund and conduct all development of palonosetron. MGI Pharma was also to pay royalties and product supply fees based upon net sales. Helalinn was to supply finished product ready for distribution [398903]. The definitive agreement was signed in April 2001 [408227].

Development history

By October 2001, patient enrollment in pivotal phase III trials of palonosetron had been completed. At this time, Helalinn expected to complete patient accrual in remaining trials in the phase III program by the end of 2001 and planned to submit an NDA in the US and Europe in the first half of 2002 [424144]. By January 2002, patient treatment had been completed and data analysis was underway. At this time, NDA submission was planned for the third quarter of 2002 [436183]. In April 2002, preliminary analysis of the pivotal phase III trials was disclosed which showed that palonosetron met the 24 h complete response primary efficacy endpoint. In addition, the complete response rate for the 24 to 120 h time period favored

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palonosetron compared to the comparator agents [448290]. In May 2002, MGI and Helsinn held a pre-NDA meeting with the FDA and confirmed that an NDA submission was planned in the third quarter of 2002 [450577]. Palonosetron was previously being developed by Syntex Corp (now Roche Bioscience) and had reached phase II trials in the US for chemotherapy-induced nausea and vomiting, but development was discontinued [382335].

Developer	Country	Status	Indication	Date	Reference
Helsinn Healthcare SA	US	Phase III	Emesis	05-APR-00	381583
Helsinn Healthcare SA	Western Europe	Phase III	Emesis	05-APR-00	381583
MGI Pharma Inc	US	Phase III	Emesis	01-APR-01	408227
MGI Pharma Inc	Western Europe	Phase III	Emesis	01-APR-01	408227
Roche Bioscience	US	Discontinued	Emesis		

Literature classifications

Chemistry

Study Type	Effect Studied	Model Used	Results	Reference
Synthetic and SAR	Describes the synthesis of analogs of ondansetron and granisetron. Palonosetron proved to be a 5-HT ₃ receptor antagonist and antiemetic. It is more potent than ondansetron and granisetron in inhibiting 5-HT ₃ receptor-induced contractions in guinea pig ileum and in blocking 5-HT ₃ receptor-induced emesis in mice.			381583
Synthetic and SAR	Describes the synthesis of analogs of ondansetron and granisetron. Palonosetron proved to be a 5-HT ₃ receptor antagonist and antiemetic. It is more potent than ondansetron and granisetron in inhibiting 5-HT ₃ receptor-induced contractions in guinea pig ileum and in blocking 5-HT ₃ receptor-induced emesis in mice.			381583

Biology

Study Type	Effect Studied	Model Used	Results	Reference
In vitro	Antagonism of contractile responses to 5-HT ₃ by ondansetron (0.1-100 nM) and palonosetron (0.1-100 nM) in guinea pig ileum (GPI) and mouse ileum (MI).	5-HT ₃ receptors mediating contraction in guinea pig ileum and mouse ileum.	Palonosetron had higher affinity for 5-HT ₃ receptors and antagonized 5-HT ₃ receptor-induced contractions more potently than ondansetron.	381583
In vitro	Antagonism of contractile responses to 5-HT ₃ by ondansetron (0.1-100 nM) and palonosetron (0.1-100 nM) in guinea pig ileum (GPI) and mouse ileum (MI).	Membranes from NG-108-15 cells, rat cerebral cortex, and guinea pig ileum.	Palonosetron exhibited higher affinity for 5-HT ₃ receptors than ondansetron.	381583
In vitro	Antagonism of contractile responses to 5-HT ₃ by ondansetron (0.1-100 nM) and palonosetron (0.1-100 nM) in guinea pig ileum (GPI) and mouse ileum (MI).	Membranes from NG-108-15 cells, rat cerebral cortex, and guinea pig ileum.	Palonosetron highly selective for 5-HT ₃ receptor, low affinity of 28 other receptors including other 5-HT receptors.	381583
In vivo	Inhibition of von Bezold-Jarisch reflex induced by 5-HT ₃ in mice.	Anesthetized rat.	Palonosetron administered IV and intradermally inhibited reflex when administered IV. Inhibition was more potent and longer lasting than ondansetron and granisetron.	381583
In vivo	Inhibition of emesis induced by apomorphine in mice.	Conscious mouse.	Palonosetron IV and po dose dependently inhibited apomorphine-induced emesis. It was more potent than ondansetron and granisetron.	381583
In vivo	Inhibition of emesis induced by apomorphine in mice.	Conscious mouse.	Palonosetron IV and po dose dependently inhibited apomorphine-induced emesis. It was more potent than ondansetron and granisetron.	381583

Metabolism

Study Type	Effect Studied	Model Used	Results	Reference
In vivo	Metabolic and pharmacokinetic profile.	Human volunteers.	Palonosetron moderately bound to plasma proteins (82%), metabolized in hepatic liver (80%), in part (40%) unchanged in the urine; elimination: 40 h (range 24.0 to 84.5 h).	410808 381583

Metabolism (continued)

Study Type	Effect Studied	Model Used	Results	Reference
In vivo	Metabolic and pharmacokinetic profile	Randomized, double-blind, parallel-group study in 37 patients with cancer scheduled to receive chemotherapy	$T_{1/2} = 2.5$ to 48.8 min, $CL_{CR} = 0.886$ to 338 mL/min, CL_{EB} (mean) $= 43.7$ to 129 mL/min, clearance 1.81 to 2.23 mL/min/kg. Kinetics dose-proportional. Well tolerated; adverse events were mild to moderate and not dose-dependent.	454078

Clinical

Effect Studied	Model Used	Results	Reference
Adverse effects	173 Healthy volunteers	Headache and constipation; incidence rates 6 and 11% higher than after placebo; not dose-related	410608 454836
Prevention of postoperative nausea and vomiting	Multi-center, randomized, double-blind, placebo-controlled, parallel-group study in 308 women and 148 men undergoing gynecologic or urologic surgery	Proportion of patients not having any nausea and not requiring anti-emetic medication after 24 hours receiving palonosetron HCl was 50% (95% CI 43-57) and 50% (95% CI 43-57), respectively, compared with 33% (95% CI 26-40) and 33% (95% CI 26-40), respectively, in the placebo group	454839
Prevention of postoperative nausea and vomiting	Randomized, double-blind, placebo-controlled, parallel-group study in 100 women undergoing gynecologic surgery	Palonosetron significantly reduced the incidence of postoperative nausea and vomiting compared with placebo (10% vs 30%, $P < 0.05$)	454840

Associated patent

Title New triazole compounds.

Assignee Syntex (USA) Inc

Publication EP-00430180 05-JUN-01

Priority US-60442682 28-NOV-98

Inventors Burger J, Clark RD, Egan RM, Smith WL, Weinhardt KC

Associated references

173464 The interaction of RS 23339-187, a potent and selective antagonist, with 5-HT₂ receptors. *In vitro*. Wong EHF, Clark R, Leung E, Leary D, Barreau DW, Johnson L, Pascoe H, Whiting RL, Egan RM *BR J PHARMACOL* 1998 114 4 981-989

• Among four antagonists, palonosetron had highest affinity for 5-HT₂ receptors mediating contraction of guinea pig isolated ileum. In NG-100-18 cell membranes, rat cerebral cortex and rat hippocampus of rabbit and guinea pig, palonosetron displayed binding of a biased selective 5-HT₂ receptor ligand but exhibited low affinity at autoreceptors, muscarinic receptors, alpha receptors, as well as 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₄ receptors.

181288 3-(Oxobutylidene-5-yl)pyridine(4,3-b)indole-1-one and isopropylidene-1-ones. Potent constitutively restricted 5-HT₂ receptor antagonists. Clark RD, Miller AB, Burger J, Rappin DS, Weinhardt KC, Kowalczyk SA, Egan RM, Barreau DW, Lee CH, Michel AD, Smith WL, Wong EHF *J MED CHEM* 1998 41 26 3845-3857

173465 Pharmacological characterization of palonosetron, a novel and selective 5-HT₂ receptor antagonist. *In vitro*. Egan RM, Lee CH, Smith WL, Johnson LB, Clark R, Whiting RL, Hargis SS *BR J PHARMACOL* 1998 114 4 980-988

• In anesthetized rats, palonosetron administered *iv*, *id* or *intracerebrally*, dose-dependently inhibited von Bezold-Jarisch reflex induced by 8-methyl-8-HT. In conscious ferrets, clonidine-induced emesis was inhibited dose-dependently by palonosetron *iv* or *po*. In conscious dogs, emesis induced by cisplatin, doxorubicin, actinomycin and methimazole was inhibited dose-dependently and more potently by palonosetron than by ondansetron.

328700 Allosteric interactions among agonists and antagonists at 5-hydroxytryptamine receptors. Barreau DW, Stadenich E, Leary DN, Hsu SAC, Egan RM, Wong EHF *J NEUROCHEM* 1998 68 1 104-110

• Binding of agonists 5-HT and 8-methyl-8-HT to unoccupied sites on 5-HT₂ receptor can increase the receptor's affinity for prebound ligands such as palonosetron and thereby slow their dissociation.

381363 Palonosetron enters phase III clinical studies for palonosetron, a new treatment for the prevention of emesis during chemotherapy. Helsin Healthcare *PRESS RELEASE* 2000 April 04

381863 Palonosetron. RS 23339, RS 23339 T07. *DRUGS RAO* 1999 2 4 252-262

381865 Total synthesis of the 5-HT₂ receptor antagonist palonosetron. Kowalczyk SA, Duvall CA *SYNTHESIS* 1998 7 519-518

• Describes the development of a short and efficient synthesis route to palonosetron.

382325 Helsin announces that patient enrollment for phase III palonosetron trials progresses both in the USA and Europe. Helsin Healthcare *PRESS RELEASE* 2000 September 14

381863 MGI Pharma signs letter of intent for exclusive license to palonosetron, a phase III antiemetic for chemotherapy-induced nausea and vomiting, from Helsin Healthcare SA. MGI Pharma Inc *PRESS RELEASE* 2001 February 19

403827 MGI Pharma signs exclusive license agreement with Helsin Healthcare SA, for palonosetron, a phase III anti-emetic. MGI Pharma Inc *PRESS RELEASE* 2001 April 10

410850 Pharmacokinetic features of a novel 5-HT₂ receptor-antagonist palonosetron (RS-23339-187). Pirozini G, Stutz R, Tsi M, Macdonald A *PROC AM SOC CLIN ONCOL* 2001 20 Abs 1898
• Reports findings concerning palonosetron's metabolic and pharmacokinetic properties as well as the safety profile of palonosetron (2.1 to 20 mg/kg).

484144 MGI Pharma and Helsin Healthcare announce the completion of patient enrollment for first palonosetron phase III pivotal trial. MGI Pharma Inc *PRESS RELEASE* 2001 October 03

426138 MGI Pharma & Helsin announce completion of pivotal phase III trial of palonosetron. MGI Pharma Inc *PRESS RELEASE* 2002 January 17

448890 MGI Pharma reports 2002 first quarter results. MGI Pharma Inc *PRESS RELEASE* 2002 April 17

480577 Palonosetron pre-NDA meeting held with FDA submission of NDA in third quarter 2001 confirmed. MGI Pharma Inc *PRESS RELEASE* 2002 May 07

482078 Palonosetron. A phase II dose ranging study to assess, over a 7-day period, the single-dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Pirozini G, Gallagher SC, Macdonald A *PROC AM SOC CLIN ONCOL* 2002 21 Abs 448
• Randomized, double-blind, parallel-group study in 37 patients with cancer scheduled to receive chemotherapy.

454655 Oral RS-25259 prevents postoperative nausea and vomiting following laparoscopic surgery. Chaffy J, Nelson T, Pollock J, Haeffler C *ANESTHESIOLOGY* 1998 88 A21
 • Multicenter, randomized, double-blind, parallel-group study in 308 females and 43 males undergoing surgery.

454656 The efficacy of RS-25259, a long-acting selective 5-HT₃ receptor antagonist, for preventing postoperative nausea and vomiting after hysterectomy procedures. Tang J, D'Angelo R, White PF, Sessler PE *ANESTH ANALG* 1998 87 2 452-457
 • Double-blind, placebo-controlled, parallel-group study in 218 females undergoing hysterectomy.

454635 An interesting 5-HT₃ receptor antagonist analgesic for patients undergoing chemotherapy-based conditioning regimens? Placidi G, Sisti R, Tai M, Chenucci G *BLOOD* 2001 98 11 Part 2 350b
 • 85% of palonosetron is protein-bound and the liver metabolizes approximately 30%, with 40% unchanged in the urine. Most frequently seen adverse effects were headache and constipation, which were neither serious nor dose-related.

455270 MGI Pharma & Helsinn announce presentation of positive palonosetron phase III trial results. MGI Pharma Inc *PRESS RELEASE* 2002 June 28

455672 Positive phase III palonosetron data show significant benefit in preventing delayed nausea and vomiting. US Biotech PAPER JAFFRAY 2002 June 28

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/EP2004/000888International filing date (day/month/year)
30.01.2004Priority date (day/month/year)
30.01.2003International Patent Classification (IPC) or both national classification and IPC
A61K31/4747, A61K9/08Applicant
HELSINN HEALTHCARE SA

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"). However, 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 68.1bis(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 three 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:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/000888

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, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 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:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable 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/EP2004/000888

Box No. II Priority

1. ☒ The following document has not been furnished:

- ☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 86.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 86.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 84.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/000888

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. 14-71

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ 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.
- ☒ no international search report has been established for the whole application or for said claims Nos. 14-71
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/000888

**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	3-12, 72,73
	No: Claims	1,2,13
Inventive step (IS)	Yes: Claims	3-12
	No: Claims	1,2,13,72,73
Industrial applicability (IA)	Yes: Claims	1-73
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

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

- 1) Although claims 1, 14, 27, 33, 46 and 59 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.
Hence, claims 1, 14, 27, 33, 46 and 59 do not meet the requirements of Article 6 PCT.
- 2) Moreover, as claims 14-71 have not been searched, the examination has only been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely for the solution disclosed in the claims 1-13, and for the methods disclosed in claims 72-73.

Re Item V

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

- 1) Reference is made to the following document:
D1: US-A-5 202 333 (BERGER JACOB ET AL) 13 April 1993, cited in the application
Unless indicated otherwise, the relevant passages are those mentioned in the search report.
- 2) Novelty (Art. 33(2) PCT)
Document D1 discloses a solution for oral administration comprising 100 to 1000 mg palonosetron in 100 ml water.
This takes away the novelty of the subject-matter of claims 1, 2 and 13.

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

International application No.

PCT/EP04/00888

3) Inventive step (Art. 33(3) PCT)

3.1 The subject-matter of claims 3-12 has been neither disclosed nor suggested in the available prior art.

3.2 Claims 73 and 72 relate to methods of filling a container with a solution of palonosetron and storing it.

The only feature distinguishing these methods from well-known ones is the composition of the palonosetron solution. Therefore, even if novelty can formally be acknowledged, the subject-matter of claims 72 and 73 does not appear to involve any inventive step.

4) All amendments should meet the requirements of Art. 34(2) PCT. Where replacement pages are filed the applicant should identify clearly all amendments made, and indicate on which passages of the original application these amendments are based (Rule 68.8(a) PCT).

Europäisches Patentamt
80286 München

München, 30 November 2004
Our Ref.: HM 5089-01WO LGM/we
Applicant: HELSINN HEALTHCARE S.A.
Serial Number: PCT/EP2004/000888

We herewith request preliminary examination of the above mentioned application. The examination shall be based on the enclosed set of claims which has been amended to overcome the objections raised in the written opinion of the International Searching Authority of 6 May 2004.

The disclosure of the new claims is as follows: new claims 1 to 13 correspond to former claims 1 to 13. New claim 14 corresponds to former claim 20. New claim 15 corresponds to former claim 18. Claim 16 corresponds to former claim 22, claim 17 corresponds to former claim 36, claim 18 corresponds to former claim 31, claim 19 corresponds to former claim 32, claim 20 corresponds to former claim 47, claim 21 corresponds to former claim 48, claim 22 corresponds to former claim 49, claim 23 corresponds to former claim 50, claim 24 corresponds to former claim 53, claim 25 corresponds to former claim 33 claim 26 corresponds to former claim 55, claim 27 corresponds to former claim 56, claims 28 and

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29 correspond to former claims 57 and 58, claim 30 corresponds to former claim 72 and claims 31 and 32 are based on former claims 12 and 13.

In the written opinion claims 14 to 71 were deemed to be not clear and concise enough. Therefore, some of these claims, as far as reasonable, have been reworded as subclaims dependent from the main claim.

In the written opinion novelty and inventive step have been acknowledged for claims 3 to 12. Novelty has been denied for claims 1, 2 and 13 with reference to US-A 5,202,333 (D1). It was held that D1 discloses a solution for oral administration comprising 100 to 1000 mg palonosetron in 100 ml water. However, this conclusion is not based on the disclosure in D1. D1 is a document describing 5-HT₃ receptor antagonist compounds which are defined by a Markush formula which comprises a multiplicity of compounds. One of this great number of compounds is palonosetron whose preparation is shown in examples 10 and 11. Example 13 of D1 is concerned with an oral formulation comprising a "compound of formula I" in an amount of 100 to 1000 mg. However, there is no definition which compound of formula I is used in the oral formulation. In the introductory part of the present application it is outlined that a lot of 5-HT₃ receptor antagonists have been known before the priority date of the present invention and have been used to treat nausea. However, higher amounts of these antagonists were necessary.

Surprisingly the inventors of the present invention found that by using a specific diastereomer falling under the general formula which is known under the name "palonosetron" it is possible to treat post operative nausea and vomiting, cancer chemotherapy induced nausea and vomiting and radiotherapy induced nausea and vomiting by using by far smaller doses as when using the 5-HT₃ antagonists of the prior art. Therefore, claim 1 is concerned with a pharmaceutically stable solution for preventing or reducing emesis which comprises a small amount of palonosetron and a pharmaceutically acceptable carrier. This preparation is not anticipated by the disclosure of D1 because D1 does not teach a pharmaceutically stable preparation which comprises palonosetron in an amount of 0,01 to about 5 mg/ml. Thus, the skilled artisan reading D1 had to make several selections to arrive at the preparation of the present invention. First of all he had to select a compound of formula I, then he had to select a diastereomer thereof and thereafter he had to select the specific range of the present

invention. There are no suggestions or incentives in D1 which would encourage the skilled artisan to use just the compound and the amount as outlined in claim 1. Therefore, D1 cannot anticipate the composition of the present invention. As there is no hint in D1 that when using palonosetron the dosage can be lowered dramatically, D1 could also not render obvious to the present invention.

As the remaining claims are all dependent from claim 1 they are patentable together with an allowable claim 1.

It is assumed that the Examiner can now accept patentability of the present application. If there are further deficiencies or objections a telephone call or the appointment of a personal interview would be highly appreciated.


(Gabriele Leisler-Gerstl)
Association No. 15

Ends.:
- new set of claims

München, 30 November 2004
Our Ref.: HM 5089-01WO LGM/wa
Applicant: HELSINN HEALTHCARE S.A.
Serial Number: PCT/EP2004/000888

CLAIMS

What is claimed is:

- 1) A pharmaceutically stable solution for preventing or reducing emesis comprising:
 - a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and
 - b) a pharmaceutically acceptable carrier.
- 2) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.02 mg/mL to about 1.0 mg/mL.
- 3) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.03 mg/mL to about 0.2 mg/mL.
- 4) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.
- 5) The solution of claim 1 comprising palonosetron hydrochloride.

- 6) The solution of claim 1 wherein the pH is from about 4.0 to about 8.0.
- 7) The solution of claim 1 wherein the pH is from about 4.5 to about 5.5.
- 8) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises a chelating agent.
- 9) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
- 10) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.
- 11) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 millimoles of a citrate buffer.
- 12) The solution of claim 1 adapted for intravenous administration.
- 13) The solution of claim 1 adapted for oral administration.
- 14) The solution of claim 11 which additionally comprises from about 0.005 to about 1.0 mg/ml EDTA.
- 15) The solution of claim 14 comprising about 0.05 mg/ml of a paroxetine hydrochloride.
- 16) The solution of claim 14 comprising from about 10 to about 40 millimoles citrate buffer.
- 17) The solution of claim 14 comprising from about 0.3 to about 0.7 mg/ml EDTA.
- 18) The solution of claim 14 adapted for intravenous administration.
- 19) The solution of claim 14 adapted for oral administration.
- 20) The solution of claim 10 wherein the mannitol is in a concentration from about 10.0 mg/ml to about 80.0 mg/ml.

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- 21) The solution of claim 20 wherein the mannitol is in a concentration from about 40.0 mg/ml to about 45.0 mg/ml.
 - 22) The solution of claim 20 wherein the palonosetron of pharmaceutically acceptable salt thereof is in a concentration from 0.01 mg/ml to about 5.0 mg/ml.
 - 23) The solution of claim 20 wherein the palonosetron of pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/ml.
 - 24) The solution of claim 20 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 millimole of a citrate buffer.
 - 25) The solution of claim 20 comprising palonosetron hydrochloride.
 - 26) The solution of claim 20 wherein the pH is from about 4.0 to about 6.0.
 - 27) The solution of claim 20 wherein the pH is from about 4.5 to about 5.5.
 - 28) The solution of claim 20 adapted for intravenous administration.
 - 29) The solution of claim 20 adapted to all administration.
 - 30) A pharmaceutically stable solution for preventing or reducing emesis comprising about 0.01 to about 0.5 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimole citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, mannitol or chelating agent and having a pH of from about 4.0 to about 6.0.
 - 31) The solution of claim 30 adapted for intravenous administration.
 - 32) The solution of claim 30 adapted for oral administration.

FORMULACIONES FARMACÉUTICAS LÍQUIDAS DE PALONOSETRON**CAMPO DE LA INVENCION**

La presente invención se relaciona con formulaciones líquidas estables de vida de almacenamiento de palonosetrón que son especialmente útiles en la preparación de medicamentos inyectables y orales.

ANTECEDENTES DE LA INVENCION

La emesis es una consecuencia devastadora de la terapia citotóxica, la radioterapia, y los ambientes post-operatorios que afectan drásticamente la calidad de vida de la gente que padece tales tratamientos. En años recientes una clase de droga denominada como antagonista receptor de 5-HT₃ (5-hidroxitriptamina) ha sido desarrollada para tratar tal emesis al antagonizar las funciones cerebrales asociadas con el receptor 5-HT₃. Ver *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 y referencias citadas aquí. Las drogas de esta clase incluyen ondansetrón, granisetron, alosetron, tropisetron, y dolasetron. Estos antagonistas 5-HT₃ son a menudo administrados intravenosamente poco antes de iniciada la quimioterapia o radioterapia, y se pueden administrar más de una vez durante el ciclo de la quimioterapia o radioterapia. Además, ellos son a menudo abastecidos como tabletas o elixires orales para suplementar una administración intravenosa, o para facilitar

el uso en casa de la droga si el paciente es auto-administrante del régimen quimioterapéutico.

En razón a que algunos agentes quimioterapéuticos pueden inducir la emesis durante periodos extendidos de varios días aún cuando a ellos se les administra solo una vez, sería deseable administrar una droga que inhibe la emesis tal como el antagonista de 5-HT₃ cada día hasta que el riesgo de emesis se haya calmado sustancialmente. La presente clase de antagonistas de 5-HT₃ no ha probado ayuda especial que cumpla esta necesidad, sin embargo, en razón a que los antagonistas receptores de 5-HT₃ comercializados habitualmente han probado ser menos efectivos para controlar la nausea y el vomito retardado ya que ellos son para controlar la emesis aguda. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, Oct. 1996; 2 (supl 1):S19-24.

Recientemente, las investigaciones clínicas que se han hecho con relación al palonosetrón, un nuevo antagonista receptor de 5-HT₃ reportado en la Patente Estadounidense No. 5,202,333. Estas investigaciones han mostrado que la droga es del orden de magnitud más potente que la mayoría de los antagonistas receptores de 5-HT₃, tiene una sorprendente vida media de aproximadamente 40 horas, y es efectiva para reducir la nausea de ataque retrasado inducida por los agentes quimioterapéuticos. Sin embargo, la formulación del palonosetrón en formulaciones líquidas ha probado ser una tarea no fácil, típicamente debido a los temas de la

estabilidad media. La patente Estadounidense ,No. 5,202,333 describe una formulación intravenosa de palonosetrón en el ejemplo 13 que contiene los siguientes ingredientes:

Ingrediente	Mg
HCl de Palonosetrón	10-100 mg.
Monohidrato de Dextrosa	q.s. para elaborar Isotónico
Monohidrato de Ácido Cítrico	1,05 mg
Hidróxido de Sodio	0,18 mg.
WFJ	A 1,0 ml.

La formulación tiene un pH de 3,7 y una estabilidad media de menos de un periodo de 1-2 años de tiempo requerido por las autoridades de salud en varios países.

El ondansetrón, sus usos, y los medicamentos hechos con andansetrón son descritos en las Patentes Estadounidenses Nos. 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, y 6,063,802. Comercialmente este es distribuido por GlaxoSmithKline como Zofran® y está indicado para la prevención de la náusea postoperatoria y el vómito (PONV), las náusea y el vómito inducidos por quimioterapia para cáncer (CINV), y la náusea y el vómito inducido por radioterapia (RINV) y está disponible como una inyección, tabletas y solución, y como Tabletas Oralmente Desintegrantes de Zofran ODT® (ondansetron).

El granisetron, sus usos, y medicamentos hechos con granisetron son descritos en las Patentes Estadounidenses Nos. 4,886,808, 4,937,247, 5,034,398, y 6,294,548. Comercialmente se distribuye por Roche Laboratorios Inc. Como Kytril® indicado para la prevencion de nausea y vomito asociado con terapia de radiacion o quimioterapia, y esta a menudo en forma de tableta, solucion oral, o como una inyeccion.

El alosetron, sus usos, y medicamentos hechos con alosetron son descritos en las Patentes Estadounidenses Nos. 5,360,800 y 6,284,770. Comercialmente este se distribuye por GlaxoSmithKline como Lotronex®.

El tropisetron esta comercialmente disponible como Navoban (Novartis) CAS-89565-68-4 (tropisetron); CAS-105826-92-4 (clorhidrato de tropisetron) y se indica para tratamiento de PONV y CINV.

El dolasetron, sus usos, y medicamentos hechos con el ondansetron son descritos en las Patentes Estadounidenses Nos. 5,011,846 y 4,906,755. Comercialmente este se distribuye por Aventis Pharmaceuticals Inc. Como Anzemet®, indicado para la prevencion tanto de PONV y CINV, y se ofrece en la forma de una tableta o una solucion intravenosa.

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Por lo tanto, subsiste la necesidad de una formulación de palonosetrón con estabilidad creciente y de esta forma vida de almacenamiento incrementada. También subsiste la necesidad de un rango apropiado de concentración tanto para el antagonista receptor 5-HT₃ como sus portadores farmacéuticamente aceptables que facilitarían la elaboración de una formulación con una estabilidad creciente.

Es un objeto de la presente invención suministrar una formulación de clorhidrato de palonosetrón con estabilidad farmacéutica creciente para evitar y/o reducir la emesis.

Es otro objeto de la invención suministrar un rango aceptable de concentraciones que estabilizará una formulación que contiene clorhidrato de palonosetrón.

Es un objeto adicional de la invención suministrar una formulación de palonosetrón que permitiría el almacenamiento prolongado.

También es objeto de la invención suministrar una formulación de palonosetrón que permitiría la esterilización terminal.

RESUMEN DE LA INVENCION

La invención tiene una serie de descubrimientos que soportan una formulación sorprendentemente efectiva y versátil para

tratamiento prevención de la emesis utilizando palonosetrón. Estas formulaciones son de duración estable durante periodos mayores de 24 meses a temperatura ambiente de cuarto, y así pueden ser almacenados sin refrigeración, y elaborados utilizando procesos no asépticos, de esterilización terminal.

En un aspecto, los inventores han descubierto las formulaciones que incluyen el ingrediente activo palonosetrón rfequieren en algunos casos solamente un décimo de la cantidad de otros compuestos previamente conocidos para tratar la emesis, que sorprendentemente permite el uso de concentraciones de palonosetrón muy inferiores a aquellas a las que ordinariamente se esperaría. Así, en una modalidad la invención suministra una solución farmacéuticamente estable para evitar o reducir la emesis que comprende a) desde aproximadamente 0,01 mg/ml a aproximadamente 5 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de ésta; y b) un portador farmacéuticamente aceptable.

Los inventores han descubierto adicionalmente que al ajustar el pH de la formulación y/o las concentraciones de excipiente es posible incrementar la estabilidad de las formulaciones de palonosetrón. Por lo tanto, en otra modalidad, la invención suministra una solución farmacéuticamente estable para evitar o reducir la emesis que comprende a) palonosetrón o una sal farmacéuticamente aceptable de ésta, b) un portador farmacéuticamente aceptable, un pH desde aproximadamente 4,0 a aproximadamente 6,0. En otra modalidad la invención

suministra una solución farmacéuticamente estable para evitar o reducir la emesis que comprende desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de ésta; desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato; y desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA.

Los inventores han descubierto adicionalmente que la adición de manitol y un agente quelante puede incrementar la estabilidad de las formulaciones de palonosetrón. Por lo tanto, en aún otra modalidad la invención suministra una solución farmacéuticamente estable para prevenir o reducir la emesis que comprende a) palonosetrón o una sal farmacéuticamente aceptable de ésta y b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable comprende un agente quelante y manitol.

DESCRIPCIÓN DETALLADA DE LA INVENCION

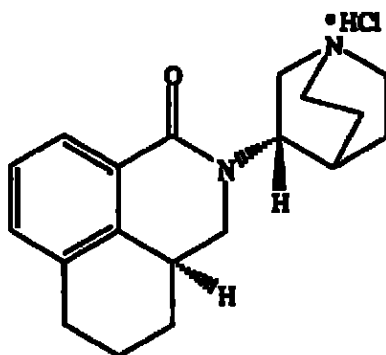
DEFINICIONES

"Frasco" significa un pequeño recipiente de vidrio sellado con el tapón y sello más adecuado, otros recipientes primarios adecuados pueden ser utilizados, por ejemplo, pero no limitados a jeringas pre-llenadas. El frasco también significa un recipiente sellado de medicamento que es

utilizado solamente una vez, e incluye frascos de vidrio rompibles y no rompibles, frascos de plástico rompibles, tarros con rosca en la punta miniatura, y cualquier otro tipo de recipiente de u tamaño capaz de mantener solamente una dosis unitaria de palonosetrón (típicamente aproximadamente 5 mls).

A lo largo de esta especificación la palabra "comprende", o las variaciones tales como "comprenden" o "que comprende", se entenderá por implicar la inclusión de un elemento establecido, entero o etapa, o grupo de elementos, enteros o etapas, pero no la exclusión de ningún otro elemento, entero o etapa, o grupo de elementos, enteros o etapas.

El "palonosetrón" significa (3aS)-2,3,3a,4,5,6-Hexahidro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-il]2,3,3a,4,5,6-hexahidro-1-oxo-1Hbenz[de]isoquinolina, y está preferiblemente presente como el monoclórhidrato. El monoclórhidrato de palonosetrón puede ser representado por la siguiente estructura química:



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Concentraciones—Cuando las concentraciones del palonosetrón son dadas aquí, la concentración se mide en términos de peso de la base libre. Las concentraciones de todos los otros ingredientes son dadas con base en el peso de los ingredientes agregados a la solución.

“Farmacéuticamente aceptable” significa lo que es útil para preparar una composición farmacéutica que es generalmente segura, no tóxica y ni biológicamente ni de otra manera indeseable e incluye aquello que es aceptable para uso veterinario así como también uso farmacéutico humano.

“Sales Farmacéuticamente aceptables” significa sales que son farmacéuticamente aceptables, como se definió anteriormente, y que poseen la actividad farmacológica deseada. Tales sales incluyen sales de adición de ácido formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, o con ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanopropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maléico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido o-(4-hidrobenczoil)benzoico, ácido cinnámico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido p-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido p-

toluenosulfónico, ácido camforsulfónico, ácido 4-metilbicyclo[2.2.2]oct-2-eno-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenobis(3-hidroxi-2-eno-1-carboxílico, ácido 3-fenilpropiónico, ácido trimetilacético, ácido terciario butilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico, y similares.

Además, las sales farmacéuticamente aceptables se pueden formar cuando un protón ácido presente es capaz de reaccionar con bases inorgánicas u orgánicas. Las bases inorgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, N-metilglucamina y similares.

DISCUSIÓN

El hecho de que el palonosetrón se pueda formular en algunos casos en concentraciones de solamente aproximadamente 1/10 de la cantidad de otros compuestos previamente conocidos para tratar la emesis, permite sorprendentemente el uso de concentraciones de palonosetrón muy por debajo de aquellas que ordinariamente se esperarían. Así, en una modalidad la invención suministra una solución farmacéuticamente estable para evitar o reducir la emesis que comprende a) desde aproximadamente 0,01 mg/ml a aproximadamente 5 mg/mL de

palonosetrón o una sal farmacéuticamente aceptable de ésta; y b) un portador farmacéuticamente aceptable. Similarmente, en otra modalidad la invención suministra un método para formular una solución farmacéuticamente estable de palonosetrón que comprende administrar desde aproximadamente 0,01 mg/mL a aproximadamente 5 mg/mL de palonosetrón o una sal farmacéuticamente aceptable de éste; con un portador farmacéuticamente aceptable. En modalidades alternativas, la formulación incluye palonosetrón o una sal farmacéuticamente aceptable de éste en una concentración desde aproximadamente 0,02 mg/mL a aproximadamente 1,0 mg/mL, desde aproximadamente 0,03 mg/mL a aproximadamente 0,2 mg/mL, y más óptimamente aproximadamente 0,05 mg/mL.

Una ventaja particular asociada con dosis inferiores de palonosetrón intravenoso es la capacidad de administrar la droga en un bolo intravenoso simple durante un periodo de tiempo corto, discreto. Este periodo de tiempo generalmente se extiende desde aproximadamente 10 a 60 segundos, o aproximadamente 10 a aproximadamente 40 segundos, y más preferiblemente es de aproximadamente 10 a 30 segundos. En una modalidad particular el palonosetrón es suministrado en frascos que comprenden 5 ml de solución, que igualan a aproximadamente 0,25 mg de palonosetrón en una concentración de aproximadamente 0,05 mg/mL.

Los inventores han descubierto adicionalmente que al ajustar el pH de la formulación y/o las concentraciones de excipiente

es posible incrementar la estabilidad de las formulaciones de palonosetrón. Por lo tanto, en otra modalidad, la invención suministra una solución farmacéuticamente aceptable para evitar o reducir la emesis que comprende a) palonosetrón o una sal farmacéuticamente aceptable de éste; y b) un portador farmacéuticamente aceptable, a un pH de aproximadamente 4,0 a aproximadamente 6,0. Similarmente, en otra modalidad la invención suministra un método para formular una solución farmacéuticamente estable de palonosetrón que comprende mezclar a) palonosetrón o una sal farmacéuticamente aceptable de ésta; y b) un portador farmacéuticamente aceptable, a un pH desde aproximadamente 4,0 a aproximadamente 6,0. En modalidades alternativas, el pH es de aproximadamente 4,5 a aproximadamente 5,5, y más óptimamente aproximadamente 5,0. Existen muchos ejemplos para aquellos expertos en la técnica de soluciones adecuadas para ajustar el pH de una formulación. Dos soluciones de ejemplo son hidróxido de sodio y solución de ácido clorhídrico, cualquiera de las cuales se podría utilizar para ajustar el pH de la formulación.

En otra modalidad la invención suministra una solución farmacéuticamente estable para evitar o reducir la emesis que comprende desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste y (i) desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato, y/o (ii) desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA. Similarmente, en otra modalidad la invención suministra un

método para formular una solución farmacéuticamente estable de palonosetrón que comprende mezclar desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste y (i) desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato, y/o (ii) desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA. El amortiguador de citrato puede estar en la forma de ácido cítrico y/o una sal de ácido cítrico tal como citrato de trisodio. En varias modalidades, los rangos de uno o más de los ingredientes anteriores pueden ser modificados como sigue:

- La formulación puede comprender palonosetrón o una sal farmacéuticamente aceptable en una concentración desde aproximadamente 0,02 mg/ml a aproximadamente 1,0 mg/ml, desde aproximadamente 0,03 mg/ml a aproximadamente 0,2 mg/ml de clorhidrato de palonosetrón, y más óptimamente aproximadamente 0,05 mg/ml.
- La formulación puede comprender amortiguador de citrato en una concentración desde aproximadamente 10 a aproximadamente 40 milimoles, o 15-30 milimoles.
- La formulación puede comprender EDTA en una concentración desde aproximadamente 0,0005 mg/ml a aproximadamente 1,0 mg/ml, o aproximadamente 0,3 a

aproximadamente 0,7 mg/ml, y más óptimamente aproximadamente 0,5 mg/ml.

Los inventores han descubierto adicionalmente que la adición de manitol y un agente quelante puede incrementar la estabilidad de formulación de palonosetrón. Por lo tanto, en aún otra modalidad de la invención se suministra una solución farmacéuticamente estable para prevenir o reducir la emesis que comprende a) palonosetrón o una sal farmacéuticamente aceptable de ésta y b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable comprende un agente quelante y manitol. Similarmente, en otra modalidad la invención suministra un método para formular una solución farmacéuticamente estable de palonosetrón que comprende mezclar a) palonosetrón o una sal farmacéuticamente aceptable de éste y b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable comprende un agente quelante y manitol. El agente quelante es preferiblemente EDTA, y, en varias modalidades el agente quelante está presente en una concentración desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml o desde aproximadamente 0,05 mg/ml a aproximadamente 1,0 mg/ml o desde aproximadamente 0,3 a aproximadamente 0,7 mg/ml, o más óptimamente aproximadamente 0,5 mg/ml. En varias modalidades el manitol está presente en una concentración desde aproximadamente 10,0 mg/ml a aproximadamente 80,0 mg/ml, desde aproximadamente 20,0 mg/ml a aproximadamente 60,0 mg/ml o desde aproximadamente 40,0 a aproximadamente 45,0 mg/ml.

Las formulaciones inyectables son típicamente formuladas como soluciones acuosas en las cuales el agua es el excipiente primario. Las formulaciones orales diferirán de las formulaciones inyectables generalmente mediante la presencia adicional de agentes saborizantes, agentes colorantes, o agentes de viscosidad. Los endulzantes naturales o sintéticos incluyen, entre otros, manitol, sorbitol, sacarosa, sacarina, aspartame, acelsulfame K, o ciclamato. Estos agentes están generalmente presentes en concentraciones en exceso de 100 mg/ml o 250 mg/ml cuando se utilizan como agentes endulzantes, como contraste a la concentración de 41,5 mg/ml de manitol descrita en algunas modalidades de la invención, en las cuales el manitol está actuando simplemente como un agente tonificante.

Las formulaciones de la presente invención son particularmente adecuadas para uso en formulaciones líquidas inyectables y orales, pero se entenderá que las soluciones pueden tener usos alternativos. Por ejemplo, ellas pueden ser utilizadas como intermedios en la preparación de otras formas de dosis farmacéuticas. Similarmente, ellas pueden tener otras rutas de administración que incluyen intranasal o inhalación. Las formulaciones inyectables pueden tomar cualquier ruta que incluye la intramuscular, intravenosa o subcutánea.

Aún las modalidades adicionales relacionan a las mejoras en el alivio con el cual la formulación de palonosetrón puede ser almacenada o elaborada. En particular, los inventores han descubierto que las formulaciones de la presente invención permiten el almacenamiento del producto durante periodos extendidos a temperatura ambiente. Así, en aún otra modalidad la invención suministra un método para almacenar uno o más recipientes en los cuales está contenida una solución de palonosetrón o una sal farmacéuticamente aceptable de éste que comprende: a) suministrar un cuarto que comprende dicho uno o más recipientes; b) ajustar o mantener la temperatura del cuarto mayor de diez, 15, o 20 grados Celsius; y c) almacenar dichos recipientes en dicho cuarto durante un mes, 3 meses, 6 meses, 1 año, 18 meses, 24 meses o más (pero preferiblemente que no sea 36 meses), en donde (i) el palonosetrón o la sal farmacéutica de éste está presente en una concentración desde aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml, (ii) el pH de la solución va desde aproximadamente 4,0 a aproximadamente 6,0, (iii) la solución comprende desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste, desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato y desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA, (iv) la solución comprende un agente quelante, o (v) la solución comprende desde aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

La estabilidad de las formulaciones anteriores también se prestan así mismas bien para los procesos de esterilización terminal en el proceso de elaboración. Por lo tanto, en aún otra modalidad la invención suministra un método para llenar un recipiente en el cual está contenida una solución de palonosetrón o una sal farmacéuticamente aceptable de éste que comprende: a) suministrar uno o más recipientes abiertos estériles (preferiblemente frascos de 5 ml); b) llenar dichos recipientes con una solución de palonosetrón en un ambiente no aséptico; c) sellar dichos recipientes llenados; y d) esterilizar dichos recipientes sellados, llenados, en donde (i) el palonosetrón o la sal farmacéuticamente aceptable de éste está presente en una concentración desde aproximadamente 0,01 mg/ml a aproximadamente 5 mg/ml, (ii) el pH de la solución va desde aproximadamente 4,0 a aproximadamente 6,0, (iii) la solución comprende desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste, desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato y desde aproximadamente 0,05 a aproximadamente 1,0 mg/ml de EDTA, (iv) la solución comprende un agente quelante, o (v) la solución comprende desde aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

EJEMPLOS

EJEMPLO 1: ESTABILIZAR EL pH

Un estudio fue conducido para determinar el efecto del pH en las formulaciones que contienen clorhidrato de palonosetrón, midiendo la estabilidad a 80° C a pH 2,0, 5,0, 7,4, y 10,0. Los resultados indicaron que el clorhidrato de palonosetrón es más estable en el pH 5,0.

EJEMPLO 2: ESTABILIZACIÓN EN LOS RANGOS DE CONCENTRACIÓN

Un estudio de optimización de formulación fue llevado a cabo usando un software de diseño experimental. Veinticuatro lotes de producto de droga fueron analizados para investigar los rangos de concentración apropiados para el clorhidrato de palonosetrón (0,05 mg/ml a 5,0 mg/ml), un amortiguador de citrato (0 a 80 mM) y EDTA (0 a 0,10%). El nivel de EDTA y el amortiguador de citrato fueron seleccionados con base en la formulación óptima, que se mostró formulada EDTA 0,05% y 20 mM de amortiguador de citrato a un pH 5,0. Los resultados de este estudio indicaron que la concentración de palonosetrón fue también un factor crítico en la estabilidad química, con una estabilidad mayor vista en las concentraciones menores de palonosetrón.

EJEMPLO 3: AGENTE DE TONIFICACIÓN

Las formulaciones de clorhidrato de palonosetrón en el amortiguador de citrato fueron preparadas incluyendo a) cloruro de sodio o b) manitol. La formulación de clorhidrato de palonosetrón que incluye el manitol mostró estabilidad

superior. El nivel óptimo de manitol requerido para una solución isotónica reencontró que era 4,15%.

EJEMPLO 4: FORMULACIÓN I

La siguiente es una formulación farmacéutica representativa que contiene palonosetrón que es útil para formulaciones intravenosas, u otras formulaciones líquidas de la droga.

Ingrediente	mg/mL
Clorhidrato de palonosetron	0,05*
Manitol	41,5
EDTA	0,5
Citrato de trisodio	3,7
Ácido cítrico	1,56
WFJ	q.s. a 1 ml
Solución de hidróxido de sodio y/o solución de ácido clorhídrico	pH 5,0 ± 0,5

*calculado como una base libre

EJEMPLO 5: FORMULACIÓN II

La siguiente es una formulación farmacéutica representativa que contiene palonosetrón que es útil para formulaciones orales, u otras formulaciones líquidas de la droga.



Ingrediente	mg/mL
Clorhidrato de palonosetron	0,05*
Manitol	150
EDTA	0,5
Citrato de trisodio	3,7
Ácido cítrico	1,56
WFJ	q.s. a 1 ml
Solución de hidróxido de sodio y/o solución de ácido clorhídrico	pH 5,0 ± 0,5
Saborizante	q.s.

*Calculado como una base libre

EJEMPLO 6—ESTABILIDAD DEL PALONOSETRÓN SIN DEXAMETASONA

La estabilidad física y química del HCl de palonosetrón fue estudiada en concentraciones de 5 µg/ml y 30 µg/ml en inyección de dextrosa al 5%, inyección de cloruro de sodio al 0,9%, dextrosa al 5% en inyección de cloruro de sodio al 0,45%, y dextrosa 5% en inyección de lactato de Ringer. Las mezclas fueron evaluadas durante 14 días a 4° C en la oscuridad y durante 48 horas a 23° C bajo luz fluorescente.

Las muestras de ensayo del HCl de palonosetrón fueron preparadas en bolsas de cloruro de polivinilo (PVC) de las soluciones de infusión en concentraciones de 5 y 30 µg/ml. Las evaluaciones en cuanto a la estabilidad física y química se llevaron a cabo sobre muestras tomadas inicialmente y

después de 1, 3, 5, 7, y 14 días de almacenamiento a 4° C y después de 1, 4, 24, y 48 horas a 23° C. La estabilidad física fue determinada usando observación visual con luz de ambiente anormal y usando un rayo de luz monodireccional de alta intensidad. En adición, la turbidez y el contenido de partículas fueron medidas electrónicamente. La estabilidad química de la droga fue evaluada usando una técnica analítica cromatográfica de líquido de alto rendimiento que indique estabilidad (HPLC).

Todas las muestras fueron estables físicamente durante el estudio. La solución permaneció clara, y hubo poco o ningún cambio en la carga de partículas y en el nivel de bruma que se hayan encontrado. Adicionalmente, hubo poca o ninguna pérdida de HCl de palonosetrón ocurrida en cualquiera de las muestras a la temperatura durante el periodo de estudio completo.

EJEMPLO 7: ESTABILIDAD DEL PALONOSETRÓN CON DEXAMETASONA

La estabilidad física y química del HCl de palonosetrón de 0,25 mg mezclada con dexametasona (como fosfato de sodio) 10 mg o 20 mg en 5% de inyección de dextrosa o 0,9% de inyección de cloruro de sodio en minibolsas de cloruro de polivinilo (PVC), y también mezcladas con dexametasona (como fosfato de sodio) 3,3 mg en 5% de inyección de dextrosa o 0,9% de inyección de cloruro de sodio en jeringas de polipropileno a 4° C en la oscuridad durante 14 días y 23° C expuesta a luz

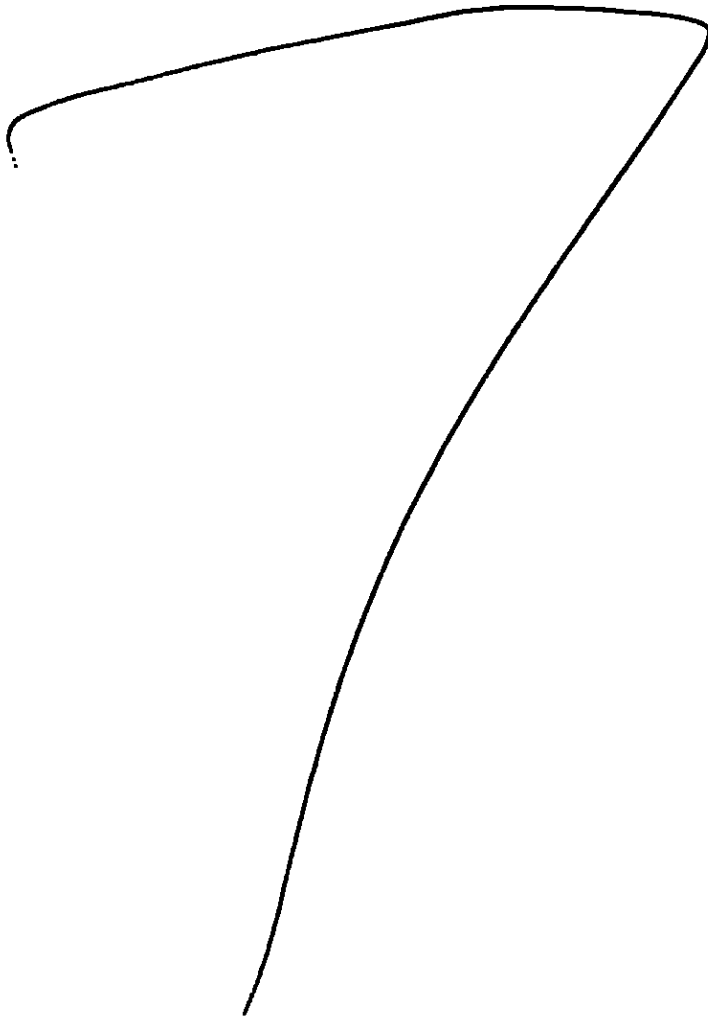
fluorescente de laboratorio normal durante 48 horas, fueron estudiadas.

Las muestras de ensayo del HCl de palonosetrón 5 µg/ml con dexametasona (como fosfato de sodio) 0,2 mg/ml y también 0,4 mg/ml fueron preparadas en minibolsas de cloruro de polivinilo (PVC) de cada solución de infusión. Adicionalmente, HCl de palonosetrón 25 µg/ml con dexametasona (como fosfato de sodio) 0,33 mg/ml en cada solución de infusión fueron preparadas como 10 ml de solución de ensayo en jeringas de propileno de 20 mL. Las evaluaciones para la estabilidad física y química se llevaron a cabo sobre muestras tomadas inicialmente y después de 1, 3, 7, y 14 días de almacenamiento a 4° C y después de 1, 4, 24, y 48 horas a 23° C. La estabilidad física fue determinada usando observación visual bajo luz de ambiente normal y usando un rayo de luz monodireccional de alta intensidad. En adición, la turbidez y el contenido de partículas fueron medidos electrónicamente. La estabilidad química de la droga fue evaluada por medio de usar la técnica analítica cromatográfica de líquido de alto rendimiento que indica estabilidad (HPLC).

Todas las muestras fueron físicamente compatibles durante todo el estudio. Las soluciones permanecieron claras, y hubo poco o ningún cambio en la carga de partículas y en el nivel de bruma que se hayan encontrado. Adicionalmente, hubo poca o ninguna pérdida de HCl de palonosetrón y dexametasona que

haya ocurrido en cualquiera de las muestras a cualquiera de las temperaturas durante el periodo completo de estudio.

Esta invención ha sido descrita con referencia a sus modalidades preferidas. Variaciones y modificaciones de la invención serán evidentes para aquellos versados en la técnica a partir de la anterior descripción detallada de la invención.



REIVINDICACIONES

Lo que se reivindica es:

1. Una solución farmacéuticamente estable para prevenir o reducir la emesis comprende:
 - a) desde aproximadamente 0,01 mg/ml a aproximadamente 5 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste; y
 - b) un portador farmacéuticamente aceptable.
2. La solución de la reivindicación 1 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración entre aproximadamente 0,02 mg/ml a aproximadamente 1,0 mg/ml.
3. La solución de la reivindicación 1 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración desde aproximadamente 0,03 mg/ml a aproximadamente 0,2 mg/ml.
4. La solución de la reivindicación 1 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración de aproximadamente 0,05 mg/ml.

5. La solución de la reivindicación 1 que comprende clorhidrato de palonosetrón.
6. La solución de la reivindicación 1 en donde el pH está entre aproximadamente 4,0 a aproximadamente 6,0.
7. La solución de la reivindicación 1 en donde el pH está entre aproximadamente 4,5 a aproximadamente 5,5.
8. La solución de la reivindicación 1 en donde el portador farmacéuticamente aceptable comprende un agente quelante.
9. La solución de la reivindicación 1 en donde el portador farmacéuticamente aceptable comprende entre aproximadamente 0,005 mg/ml a aproximadamente 1,0 mg/ml de EDTA.
10. La solución de la reivindicación 1 en donde el portador farmacéuticamente aceptable comprende manitol.
11. La solución de la reivindicación 1 en donde el portador farmacéuticamente aceptable comprende entre aproximadamente 10 a aproximadamente 1000 milimoles de un amortiguador de citrato.

12. La solución de la reivindicación 1 adaptada para administración intravenosa.
13. La solución de la reivindicación 1 adaptada para administración oral.
14. Una solución farmacéuticamente estable para prevenir o reducir la emesis comprende:
 - a) Palonosetrón o una sal farmacéuticamente aceptable de éste; y
 - b) un portador farmacéuticamente aceptable, a un pH que está entre aproximadamente 4,0 a aproximadamente 6,0.
15. La solución de la reivindicación 14 en donde el pH está entre aproximadamente 4,5 a aproximadamente 5,5.
16. La solución de la reivindicación 14 en donde el pH es aproximadamente 5,0.
17. La solución de la reivindicación 14 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración entre aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml.

18. La solución de la reivindicación 14 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración de aproximadamente 0,05 mg/ml.
19. La solución de la reivindicación 14 en donde el portador farmacéuticamente aceptable comprende un agente quelante.
20. La solución de la reivindicación 14 en donde el portador farmacéuticamente aceptable comprende entre aproximadamente 0,005 mg/ml a aproximadamente 1,0 mg/ml de EDTA.
21. La solución de la reivindicación 14 en donde el portador farmacéuticamente aceptable comprende manitol.
22. La solución de la reivindicación 14 en donde el portador farmacéuticamente aceptable comprende entre aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.
23. La solución de la reivindicación 14 que comprende clorhidrato de palonosetrón.

24. La solución de la reivindicación 14 que comprende adicionalmente hidróxido de sodio o ácido clorhídrico.
25. La solución de la reivindicación 14 adaptada para administración intravenosa.
26. La solución de la reivindicación 14 adaptada para administración oral.
27. Una solución farmacéuticamente estable para impedir o reducir la emesis comprende:
- a) desde aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste;
 - b) desde aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato; y
 - c) desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA.
28. La solución de la reivindicación 27 que comprende aproximadamente 0,05 mg/ml de clorhidrato de palonosetrón.

29. La solución de la reivindicación 27 que comprende desde aproximadamente 10 a aproximadamente 40 milimoles del amortiguador de citrato.
30. La solución de la reivindicación 27 que comprende desde aproximadamente 0,3 a aproximadamente 0,7 mg/ml de EDTA.
31. La solución de la reivindicación 27 adaptada para administración intravenosa.
32. La solución de la reivindicación 27 adaptada para administración oral.
33. Una solución farmacéuticamente estable para impedir o reducir la emesis comprende:
- a) palonosetrón o una sal farmacéuticamente aceptable de éste y
 - b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable comprende un agente quelante.
34. La solución de la reivindicación 33 en donde el agente quelante es EDTA.

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35. La solución de la reivindicación 33 en donde el agente quelante está presente en una cantidad desde aproximadamente 0,005 mg/ml a aproximadamente 1,0 mg/ml.
36. La solución de la reivindicación 33 en donde el agente quelante está presente en una cantidad desde aproximadamente 0,3 mg/ml a aproximadamente 0,7 mg/ml.
37. La solución de la reivindicación 33 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración desde aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml.
38. La solución de la reivindicación 33 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración de aproximadamente 0,05 mg/ml.
39. La solución de la reivindicación 33 en donde el portador farmacéuticamente aceptable comprende manitol.
40. La solución de la reivindicación 33 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

41. La solución de la reivindicación 33 que comprende clorhidrato de palonosetrón.
42. La solución de la reivindicación 33 en donde el pH está entre aproximadamente 4,0 a aproximadamente 6,0.
43. La solución de la reivindicación 33 en donde el pH está entre aproximadamente 4,5 a aproximadamente 5,5.
44. La solución de la reivindicación 33 adaptada para administración intravenosa.
45. La solución de la reivindicación 33 adaptada para administración oral.
46. Una solución farmacéuticamente estable para impedir o reducir la emesis comprende:
 - a) palonosetrón o una sal farmacéuticamente aceptable de éste y
 - b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable comprende manitol.
47. La solución de la reivindicación 46 en donde el manitol está en una concentración desde

aproximadamente 10,0 mg/ml a aproximadamente 80,0 mg/ml.

48. La solución de la reivindicación 46 en donde el manitol está en una concentración desde aproximadamente 40,0 mg/ml a aproximadamente 45,0 mg/ml.

49. La solución de la reivindicación 46 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración desde aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml.

50. La solución de la reivindicación 46 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración de aproximadamente 5,0 mg/ml.

51. La solución de la reivindicación 46 en donde el portador farmacéuticamente aceptable comprende un agente quelante.

52. La solución de la reivindicación 46 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 0,005 mg/ml a aproximadamente 1,0 mg/ml de EDTA.

53. La solución de la reivindicación 46 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.
54. La solución de la reivindicación 46 que comprende clorhidrato de palonosetrón.
55. La solución de la reivindicación 46 en donde el pH está entre aproximadamente 4,0 a aproximadamente 6,0.
56. La solución de la reivindicación 46 en donde el pH está entre aproximadamente 4,5 a aproximadamente 5,5.
57. La solución de la reivindicación 46 adaptada para administración intravenosa.
58. La solución de la reivindicación 46 adaptada para administración oral.
59. Una solución farmacéuticamente estable para impedir o reducir una emesis inducida por la droga comprende
- a) palonosetrón o una sal farmacéuticamente aceptable de éste y
 - b) un portador farmacéuticamente aceptable, en donde el portador farmacéuticamente aceptable

comprende entre 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

60. La solución de la reivindicación 59 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 10 a aproximadamente 70 milimoles de un amortiguador de citrato.
61. La solución de la reivindicación 59 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 10 a aproximadamente 40 milimoles de un amortiguador de citrato.
62. La solución de la reivindicación 59 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración desde aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml.
63. La solución de la reivindicación 59 en donde el palonosetrón o la sal farmacéuticamente aceptable de éste está en una concentración de aproximadamente 0,05 mg/ml.
64. La solución de la reivindicación 59 en donde el portador farmacéuticamente aceptable comprende un agente quelante.

65. La solución de la reivindicación 59 en donde el portador farmacéuticamente aceptable comprende desde aproximadamente 0,005 mg/ml a aproximadamente 1,0 mg/ml de EDTA.
66. La solución de la reivindicación 59 en donde el portador farmacéuticamente aceptable comprende manitol.
67. La solución de la reivindicación 59 que comprende clorhidrato de palonosetrón.
68. La solución de la reivindicación 59 en donde el pH está entre aproximadamente 4,0 a aproximadamente 6,0.
69. La solución de la reivindicación 59 en donde el pH está entre aproximadamente 4,5 a aproximadamente 5,5.
70. La solución de la reivindicación 59 adaptada para administración intravenosa.
71. La solución de la reivindicación 59 adaptada para administración oral.
72. Un método para almacenar uno o más contenedores en los cuales están contenidas una solución de palonosetrón o una sal farmacéuticamente aceptable de éste comprende:

- a) suministrar un cuarto que comprende dicho uno o más contenedores;
- b) ajustar o mantener la temperatura del cuarto mayor de aproximadamente 10° Celsius;
- c) almacenar dichos contenedores en dicho cuarto durante un mes o más,

en donde (i) el palonosetrón o la sal farmacéutica de éste está presente en una concentración de aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml, (ii) el pH de la solución está entre aproximadamente 4,0 a aproximadamente 6,0, (iii) la solución comprende entre aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste, desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato y desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA, (iv) la solución comprende manitol o un agente quelante, o (v) la solución comprende entre aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

73. Un método para llenar un contenedor en el cual estará contenida una solución de palonosetrón o de una sal farmacéuticamente aceptable de éste comprende:

- a) suministrar uno o más contenedores estériles abiertos;
- b) llenar dichos contenedores con una solución de palonosetrón en un ambiente no aséptico;
- c) sellar dichos contenedores llenos; y
- d) esterilizar dichos contenedores llenos y sellados,

en donde (i) el palonosetrón o la sal farmacéutica de éste está presente en una concentración entre aproximadamente 0,01 mg/ml a aproximadamente 5,0 mg/ml, (ii) el pH de la solución está entre aproximadamente 4,0 a aproximadamente 6,0, (iii) la solución comprende entre aproximadamente 0,01 a aproximadamente 5,0 mg/ml de palonosetrón o una sal farmacéuticamente aceptable de éste, desde aproximadamente 10 a aproximadamente 100 milimoles de amortiguador de citrato y desde aproximadamente 0,005 a aproximadamente 1,0 mg/ml de EDTA, (iv) la solución comprende manitol o un agente quelante o manitol, o (v) la solución comprende entre aproximadamente 10 a aproximadamente 100 milimoles de un amortiguador de citrato.

RESUMEN

La presente invención se relaciona con formulaciones líquidas estables al almacenamiento de palonosetrón para reducir la emesis inducida por quimioterapia y radioterapia con palonosetrón. Las formulaciones son particularmente útiles en la preparación de medicamentos líquidos intravenosos y orales.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 53,298
FECHA : JULIO 18 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicación : 05071968 00000000 Folios: 129
Fecha (AMD): 27/05-07-29 17:35:45
Trámite : 011 PCT-PATENT 379 FASE NINCI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	31589394	18/07/2005	53,445,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

06 14811- 841-001-9

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	()
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 o 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 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** ()

Firma Responsable



Fecha

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO

REFERENCIA	Radicación No.	5 74968
	Solicitud internacional	EP2004/000888
	Fecha inicio fase nacional	30/08/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	

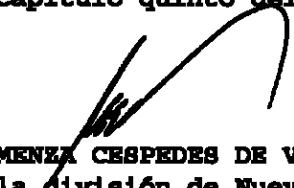
9460

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:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.
2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.
3. La solicitud no contiene el poder debidamente otorgado, con el lleno de los 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 ésta fuere 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 Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 19.4 OCT. 2005
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