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SUPERINTENDENCIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

**SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

**REF: SOLICITUD No. : 00058156
SOLICITANTE : LILLY ICOS LLC.
FECHA SOLICITUD : AGOSTO 2, 2000
PATENTE : PRODUCTOS FARMACEUTICOS CON β -CARBOLINA**

SOLICITUD DE ESTUDIO DE FONDO

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial N°.520 de fecha Septiembre 27 de 2002 se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente.

Agradezco continuar con el presente trámite.

Señor Jefe,

**DILIA RODRIGUEZ D' ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.**

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Industria y Comercio

SUPERINTENDENCIA

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***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
	TOTAL :	\$ 318,000.00

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-58156

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION FUE PUBLICADO EN

LA GACETA DE PROPIEDAD INDUSTRIAL No 520, DE FECHA 27 DE SEPTIEMBRE DE 2002, EL

TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 26 DE DICIEMBRE DE 2002.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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(54) Modafinil composition of defined particle size

(57) Pharmaceutical compositions comprising a substantially homogeneous mixture of modafinil particles wherein at least about 95% of total particles have a diameter of less than about 200 microns. Preferably the particles are in the size range 2 - 80 microns. The composition may be in the form of a tablet, capsule, powder, pill, liquid/suspension or emulsion.

ACETAMIDE DERIVATIVE HAVING DEFINED PARTICLE SIZEBACKGROUND OF THE INVENTION

5 This invention relates to the acetamide derivative modafinil. Modafinil ($C_{15}H_{15}NO_2S$), is 2-(benzhydryl-sulfinyl)acetamide, and is also known as 2-[(diphenylmethyl) sulfinyl] acetamide.

 Modafinil has been described as presenting a
10 "neuropsychopharmacological spectrum characterized by the presence of excitation with hyperactivity and of hypermotility; and by the absence of stereotypy (except in high doses) and of potentialisation of the effects of apomorphine and amphetamine" (U.S. Patent 4,177,290;
15 hereinafter the "'290 patent," which is incorporated herein by reference). A single administration of modafinil results in increased locomotor activity in mice and increased nocturnal activity in monkeys (Duteil et al., *Eur. J. Pharmacol.* 180:49 (1990)). The
20 neuropsychopharmacological profile of modafinil has been distinguished from that of amphetamines (Saletu et al., *Int. J. Clin. Pharm. Res.* 2:183 (1989)). Modafinil is thought to modulate the central postsynaptic
25 dopaminergic system (Duteil et al., supra). Modafinil has been successfully tested in humans for treatment of idiopathic hypersomnia and narcolepsy (Bastuji et al., *Prog. Neuro-Psych. Biol. Psych.* 12:695 (1988)).

 Narcolepsy is a chronic disorder characterized by
30 intermittent sleep attacks, persistent, excessive daytime sleepiness and abnormal rapid eye movement ("REM") sleep manifestations, such as sleep-onset REM periods, cataplexy, sleep paralysis and hypnagogic hallucinations, or both (Assoc. of Sleep Disorders Centers, Sleep 2:1

SUMMARY OF THE INVENTION

Our invention discloses a pharmaceutical composition comprising modafinil in the form of particles of a defined size, and the use of such composition. We have discovered that the size of modafinil particles is important to the potency and safety profile of the drug. "Particle," as used herein, refers to an aggregated physical unit of the acetamide compound, i.e., a piece or a grain of acetamide. For example, Figures 2-5 provide photographic representations of various modafinil particles from Lots E-D and L-1.

As used herein, the term "mean," when used in reference to the size of modafinil particles, refers to the sum of the size measurements of all measurable particles measured divided by the total number of particles measured. For example, for five measurable particles which could be measured, and were determined to have diameters of 20 microns, 23 microns, 20 microns, 35 microns and 20 microns, the mean diameter would be 23.6 microns. As used herein, the term "diameter" is a volumetric measurement based on the presumed spherical shape of modafinil particles.

As used herein, the term "median," when used in reference to the size of modafinil particles, indicates that about 50% of all measurable particles measured have a particle size less than the defined median particle size value, and that about 50% of all measurable particles measured have a particle size greater than the defined median particle size value. For example, for the five particle values listed above, the median diameter would be 20 microns.

As used herein, the term "mode," when used in reference to the size of modafinil particles, indicates the most frequently- occurring particle size value. For example, for the five particle values listed above, the

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Lot L-1 (median particle size 50.18 μm).

Fig. 8 is a graph depicting mean plasma concentration of modafinil in dogs following single oral doses of modafinil from lots with different particle sizes.

Fig. 9 is a graph depicting mean plasma concentration of modafinil equivalents, i.e., modafinil and modafinil acid metabolite, in dogs, following single oral doses of modafinil from lots with different particle sizes.

II. The Invention

The invention results from our discovery that the particle size, and the consistency of the particle size, of modafinil can have a significant effect on its potency and safety profile.

The first human trials for the use of modafinil to treat narcolepsy took place outside of the United States of America. The modafinil used in the initial studies was prepared in non-commercial scale lots (referred to herein as "early" or "E" lots). Pursuant to our discovery of the present invention, it was observed that the early lots had a median particle size of between 80 microns (" μm ") and 150 μm . In the initial safety studies conducted outside of the United States, early lot modafinil was administered to humans without reports of clinically significant adverse events in acute administration.

Separate safety and efficacy studies of modafinil were subsequently conducted in the United States under the direction of Cephalon, Inc. using modafinil lots prepared by a method scaled up for commercial production (referred to herein as "late" or "L" lots). When the late lots of modafinil were administered to humans in the United States, the initial clinical trial revealed the

Table 1
MODAFINIL PARTICLE DIAMETER

LOT	MEAN* (μm)	MEDIAN* (μm)	MODE* (μm)	STD DEVIATION BETWEEN MEAN, MEDIAN, MODE	MEDIAN:M EAN:MODE
E-A	34.60 +/- 5.21	143.65 +/- 3.26	176.48 +/-5.32	74.27	1:4.15:. 81
E-B	29.99 +/-1.09	89.10 +/-4.28	78.59 +/- 2.60	31.53	1:2.97:1 .13
E-C	28.27 +/- 4.10	79.00 +/- 3.78	101.00 +/- 40.92	37.30	2:2.79:. 78
E-D	22.14 +/- 0.76	94.05 +/- 13.75	158.63 +/- 63.81	68.28	1:4,25:. 59
L-1	21.40 +/- 2.52	50.18 +/- 12.57	56.56 +/- 22.39	18.73	1:2.34:. 89
L-2	18.75 +/- 1.89	31.41 +/- 3.57	25.31 +/- 1.34	6.36	1:1.68:1 .24

*n=4; +/- values are standard deviations

Fig. 1 is a graph of particle diameter versus percent cumulative particles for late Lots L-1, L-2, and for the early Lots E-A, E-B, E-C, and E-D. The 50 percent cumulative particle size for Lots L-1 and L-2 was between approximately 30 μm and approximately 50 μm, while the 50 percent cumulative particle size for Lots E-A, E-B, E-C, and E-D was between approximately 80 μm and approximately 140 μm.

In addition to the Hiac/Royko data, electron microscopy and optical microscopy were used to verify modafinil particle size and morphology. Representative scanning electron micrographs of early Lot E-D are shown in Fig. 2 (50x magnification) and in Fig. 3 (100x magnification). Representative scanning electron micrographs of late Lot L-1 are shown in Fig. 4 (50x magnification) and Fig. 5 (100x magnification).

It is noted that the size of modafinil particles may be determined by any of several conventional methods. Methods useful for analyzing particle size within the range of 100 Angstroms to 100 μm , include, but are not limited to: laser diffraction particle size analysis, mechanical sieving, optical microscopy, ultracentrifugation, sedimentation, air permeability, electron microscopy, scanning electron microscopy and Coulter Counter techniques. For a general review of methods for determining particle size, see Martin et al., Physical Pharmacy, 3rd Ed., Lea & Febiger, Philadelphia (1983). See also O'Conner in Remington's, infra., Section IX.

Optical microscopy is useful for particle size measurement in the range of 0.2 μm to 100 μm . For optical microscopy, an emulsion or suspension, diluted or undiluted, is mounted on a slide or ruled cell. The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated.

Mechanical sieving uses a series of standard sieves calibrated by the National Bureau of Standards. Mechanical sieves may be used for screening material as fine as 44 μm (No. 325 sieve). Sieves manufactured by photo-etching and electroforming are available with apertures from 90 μm to 5 μm .

Measurements obtained using instruments and techniques developed by Hiac/Royko are preferred. A Hiac/Royco sizing counter utilizes the principle of light-extinction (obscuration) for particle size detection. The principle involved is that when a particle suspended in a liquid passes through a sensor microcell where a laser beam is directed through a window at the cell, the particles in the fluid block the laser beam from a light-extinction photodiode (photodetector) resulting in a loss of light intensity. This loss of

light intensity detected by the photodetector produces an electrical pulse for each particle. These pulses are proportional in amplitude to the light intensity (light extinction) which is a measure of particle size.

5 VII. Effect of Modafinil Particle Size on Rate of Modafinil Dissolution

We investigated the effect of modafinil particle size on the rate of dissolution. The results of those experiments are summarized in Fig. 6 and Fig. 7.

10 In the first experiment, 500 ml of deionized water was put in a 1-liter beaker and 50 mg of E-D or L-1 was added. The suspension was stirred constantly with a 5 cm Teflon-coated magnetic stir bar and a magnetic stir plate (Thermolyne model # 546725). Samples of 1 ml each were
15 taken at times 0, 1, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes, with each sample being replaced with 1 ml of deionized water. The stir plate speed setting was "2" for the first 20 minutes, and "7" from 20 to 60 minutes. Each sample was immediately filtered through a 0.45µm
20 filter, to remove undissolved particles. The filtered samples were assayed for modafinil, by high performance liquid chromatography, based upon the method of Moachon et al. (J. Chromatag. B 654:91 (1994)). Modafinil Lot L-1 (median: 50.18 µm) had a faster dissolution rate than
25 did modafinil Lot E-D (mean: 94.05 µm). The results of the first experiment are summarized in Fig. 6.

A second dissolution rate experiment was conducted to determine relative dissolution rates of modafinil from the capsules used in the dog study (described below) of
30 plasma modafinil levels following oral administration of modafinil from Lots E-B, E-D and L-1. In the second dissolution rate experiment, the solvent was 900 ml of 0.01 N HCl, maintained at 37°C. Each sample placed into the solvent consisted of 200 mg of modafinil packed in a
35 gelatin capsule. Stainless steel coils were attached to

the capsules to prevent them from floating. A stirring paddle was used at 100 rpm. Solution samples were taken at 0, 5, 10, 15, 20, 25, 30, 40 and 60 minutes. The results of the modafinil capsule dissolution experiment are summarized in Fig. 7.

VIII. Effect of Modafinil Particle Size on Modafinil Plasma Concentration

Given the disparity in results between the foreign and United States studies using what was presumed to be "identical" modafinil, additional non-human analyses were necessary prior to continuation of human clinical trials. Accordingly, animal studies in dogs were carried out to determine the in vivo pharmacokinetics of modafinil with different average particle size diameters, roughly designated as having "small" (Lot L-1) and "large" (Lots E-B and E-D) median particle sizes. Nine male dogs were randomly assigned, according to body weight to three dose groups. Each group was given a single oral dose of 200 mg modafinil weekly for three weeks in a randomized, cross-over design, as described in Table 2.

Table 2

	GROUP	NUMBER OF DOGS	WEEK	BULK DRUG LOT AND MEDIAN PARTICLE SIZE
25	1	3	1	E-D (94.05 μ m)
			2	L-1 (50.18 μ m)
			3	E-B (89.10 μ m)
30	2	3	1	L-1 (50.18 μ m)
			2	E-B (89.10 μ m)
			3	E-D (94.05 μ m)
35	3	3	1	E-B (89.10 μ m)
			2	E-D (94.05 μ m)
			3	L-1 (50.18 μ m)

After each weekly dose, blood samples (2 ml) were drawn from all animals by venepuncture predose (within

one hour of dosing), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, and 36 hours post-dose. Blood samples were collected in heparinized (lithium heparin) test tubes and centrifuged at 2,500 to 3,000 rpm. The plasma was drawn
5 off with a glass pipette, and stored frozen (-20 C) until analyzed. The plasma concentration of modafinil, and its acid and sulfone metabolites were simultaneously determined by high-pressure liquid chromatography, according to the method of Moachon et al. (J. Chromatog.
10 B 654:91 (1994)).

Mean plasma modafinil levels in the nine dogs, at 0 to 36 hours after modafinil administration, are depicted in Fig. 8. With "small" particles (Lot L-1), the plasma modafinil concentration peaked at 10 µg/ml.
15 In contrast, with "larger" particles (Lots E-D or E-B), the plasma modafinil concentration peaked at 8 µg/ml. Thus, the modafinil having a median particle size of 50.18 µm resulted in a higher peak plasma concentration than that obtained with the same dose of modafinil
20 administered in the form of larger particles. Similar results were observed regarding the acid metabolite of modafinil, 2-benzhydrylsulfinylacetic acid as depicted in Fig. 9.

These results implicated the consequences of
25 different particle sizes and the importance of controlling modafinil particle size. By controlling the particle size, safety concerns can be addressed. For example, a non-homogenous mixture of modafinil particle sizes may not provide consistent potency nor avoid
30 undesired fluctuations in plasma modafinil concentrations; such fluctuations can lead to undesired and unexpected events. Moreover, the use of modafinil particles having a defined size is more efficient because a given plasma modafinil concentration can be achieved at
35 a lower oral dose.

After the discrepancy between the foreign and first United States studies was resolved and determined to be related to the differences in particle sizes, a second Phase I study was conducted in the United States, to further determine the clinical safety, tolerance and pharmacokinetic properties of modafinil having a particle size as defined. The second study involved normal young males and an experimental design similar to the first United States study (described above).

In the second study, all subjects began at 200 mg/day using modafinil from Lots L-1 or L-2. Dosage was then titrated, in 200 mg/day increments, up to the target dose. The results of this study suggested that 600 mg/day was the maximum tolerable dose ("MTD") of modafinil, with 800 mg/day being the minimum intolerable dose.

IX. Methods of Preparing Modafinil Having Defined Size

Modafinil and modafinil-related compounds can be prepared by conventional methods. Methods for preparing modafinil and modafinil-related compounds appears in the '290 patent. Modafinil of the particle size defined herein may be obtained by a variety of approaches utilizing conventional methods, e.g., the methods disclosed in the '290 patent, and then subjecting the modafinil of undefined particle size to conventional methods of milling and sieving. Methods for comminution (i.e., the mechanical process of reducing the size of particles or aggregates) are known to those in the art. Examples are provided in O'Conner et al. Chpt. 88, Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., Easton, PA (1990). Following comminution, the particles can be separated into a series of sieve cuts by passing the particles downward through

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an agitated vertical stack of sieves of decreasing mesh sizes and collecting the granules retained on each sieve or in the bottom pan. Particles which fall outside of a desired range can again be subjected to milling and
5 sieving.

X. Formulation and Administration

An appropriate dosage for modafinil having a defined particle size is between about 50 mg and about 700 mg of modafinil.

10 The pharmaceutical composition described herein is most preferably administered orally in the form of a vehicle such as a tablet, capsule, powder, pill, liquid/suspension or emulsion. The administration vehicle may comprise a pharmaceutically- acceptable
15 carrier. The carrier may comprise agents that aid solubility, absorption, flavor, color or texture of the vehicle or its contents. Topical administration via an epidermal patch or the like, or administration via direct injection of the drug, is also acceptable. A vehicle of
20 the invention can include $\pm 10-15\%$ of the modafinil particle, due to factors such as vehicle manufacturing tolerances and expected shelf life of the modafinil. For example, a vehicle labeled as containing 50 mg can be initially prepared with, e.g., 55 or 58 mg of modafinil,
25 with the expectation that after one month to two years of storage, the active amount of modafinil therein has decreased. Vehicles prepared with such adjustments in order to compensate for the expected degradation of the drug fall within the scope of the invention.

30 While the invention has been described in considerable detail, the invention disclosed herein is not to be limited to the actual description, but is to be afforded the full scope of the appended claims and all equivalents thereto. Although the specific examples
35 presented herein are directed to the use of modafinil of

1. A pharmaceutical composition comprising a substantially homogeneous mixture of modafinil particles, wherein at least about 95% of the cumulative total of
5 modafinil particles in said composition have a diameter of less than about 200 microns (μm).

2. The composition of claim 1 wherein said particles have a median diameter range of between about
10 $2\mu\text{m}$ and about $60\mu\text{m}$.

3. The composition of claim 1, wherein said composition comprises between about 50 milligrams and about 700 milligrams of said modafinil.

4. A pharmaceutical composition substantially as hereinbefore described with reference to the accompanying drawings.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP96/02299 (22) International Filing Date: 30 May 1996 (96.05.96) (30) Priority Date: 9511220.7 2 June 1995 (95.06.95) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED (GB/GB); Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlessex UB6 0NN (GB). (72) Inventor: and (73) Inventor/Applicant (for US only): BUTLER, James, Matthew (GB/GB); Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). (74) Agents: GALLAFENT, Alison et al.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlessex UB6 0NN (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, JP, KR, KZ, KP, KR, KZ, LA, LB, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AR, IP, patent (KR, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: METHOD OF PRODUCING A SOLID DISPERSION OF A POORLY WATER SOLUBLE DRUG (57) Abstract Solid dispersions of poorly soluble drugs, to processes for their preparation and their use in pharmaceutical compositions. Specifically, solid dispersions of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrimido[2',1':6,1]pyrido[3,4-b]indole-1,4-dione and (+)-N-[1-(adamantanemethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylbenzene are described.		

Pharmac., 1976, 28 601, describes co-precipitation of trifluoperazine embonate and the polymers poly DL-aspartic acid and polymethylmethacrylate. The co-precipitates were prepared by dissolving the drug and polymer in dimethylformamide and adding the solution to a rapidly stirred volume of water. Both polymers and drug are insoluble in water.

In general terms, problems which can be associated with known co-precipitation techniques can include excess solvent usage, identifying carrier/drug combinations which can be effectively precipitated and enhance bioavailability, the use of heat to effect solution which may detrimentally affect the drug, and the like. Co-precipitation techniques are however attractive for the preparation of solid dispersions, in that less solvents and heat are employed when compared to techniques such as co-evaporation and solvent removal may therefore be facilitated.

We have now developed a co-precipitation technique which alleviates the above described disadvantages associated with known techniques, and have also found that co-precipitation offers an advantageous preparation route for solid dispersions of poorly water soluble drugs.

There is therefore provided in a first aspect of the present invention a process of preparing a solid dispersion comprising a poorly water soluble drug or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

- (I) providing an intimate mixture comprising the carrier or excipient and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water;
- (II) co-mixing the intimate mixture obtained in step (I) with a poorly water soluble drug; and
- (III) co-precipitating the poorly water soluble drug and the carrier or excipient.

As used herein, the term "intimate mixture" can denote a solution, suspension, emulsion, colloid, dispersion or the like. Generally, the term "intimate mixture" as used herein denotes a solution.

5 It has been found surprisingly that small amounts of water in the intimate mixture can aid dissolution of the subsequently added poorly water soluble drug. For example, a 10% ratio of water in a solvent may aid dissolution of the poorly water soluble drug.

10 In a further aspect, the invention describes a process of preparing a solid dispersion comprising a particular cGMP specific PDE (PDEV) inhibitor. More particularly, co-precipitation overcomes problems associated with other preparatory processes for formulating the subject PDEV inhibitor.

15 There is therefore provided by the present invention a process of preparing a solid dispersion comprising (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione }
(hereinafter referred to as Compound A) or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which
20 process comprises co-precipitating Compound A and the pharmaceutically acceptable carrier or excipient.

In a yet further aspect, the invention describes a process of preparing a solid dispersion comprising a particular gastrin and CCK-B antagonist. More
25 particularly, co-precipitation overcomes problems associated with other preparatory processes for formulating the subject gastrin and CCK-B antagonist.

There is therefore provided by the present invention a process of preparing a solid dispersion comprising (+)-N-[1-(Adamantanemethyl)-2,4-dioxo-5-phenyl-
30 2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea (hereinafter referred to as Compound B) or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises co-precipitating Compound B and the pharmaceutically acceptable carrier or excipient. The synthesis and use of Compound B has been previously
35 described in WO93.14074.

Suitably the co-precipitation of Compound A or B comprises the steps of:

5 (a) providing an intimate mixture of a poorly water soluble drug selected from Compound A or Compound B, the carrier or excipient therefor and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water; and

10 (b) co-precipitating the compound and the carrier or excipient.

15 It is generally advantageous in step (a) to first co-mix the carrier or excipient together with the solvent or solvents and optional water, thereby providing an initial intimate mixture, prior to addition of the poorly water soluble drug thereto. Subsequently, the drug can be added to the initial intimate mixture. Optionally, the carrier or excipient and solvent initial intimate mixture can be subjected to heating sufficient to facilitate dissolving of the former in the latter. Such a sequence of steps (also substantially as hereinbefore described according to the first aspect of the present invention) can be beneficial in allowing the employ of heat to effect dissolving, whilst obviating any detrimental affect by the heat on the drug.

20 A co-precipitation step, substantially as described in step (iii), or substantially as described in step (b), can aptly comprise adding the drug, carrier or excipient and solvent to a co-precipitation medium in which the carrier or excipient is insoluble. The resultant co-precipitate can be separated from the remaining components, suitably by filtering or the like, and the co-precipitate washed to remove residual solvent, and dried. The co-precipitate can then be formulated in a suitable pharmaceutical form employing known formulatory techniques, substantially as hereinafter described.

30 The carrier or excipient for the drug, and the co-precipitation medium, are respectively chosen so that the carrier or excipient is substantially insoluble in the co-precipitation medium. It is also advantageous that the carrier or excipient has selected dissolution properties in vivo; for example, the carrier or excipient may be such so as to dissolve rapidly (within about 15 to 60 minutes) in vivo.

123 119

6

alternatively the carrier or excipient may be such so as to dissolve over a relatively prolonged period of time (typically, 2 to 4 hours) so as to achieve sustained release of drug in vivo.

5 Suitable carrier or excipients include pharmaceutically acceptable polymeric materials, typical examples being hydroxypropyl methyl cellulose phthalate, polymethylacrylate, hydroxypropyl cellulose and other like carrier or excipient materials. Particularly preferred is hydroxypropyl methyl cellulose phthalate as a carrier or excipient, and there is further provided by the present invention co-precipitates consisting of Compound A and hydroxypropyl methyl cellulose phthalate, and Compound B and hydroxypropyl methyl cellulose phthalate.

15 Aptly the co-precipitation medium comprises an aqueous medium, which is optimally such that the carrier or excipient is substantially insoluble therein as substantially hereinbefore described.

20 Conveniently the following combinations of carrier or excipient and co-precipitation medium can be employed in a process according to the present invention:

25 (a) in the case where the carrier or excipient is hydroxypropyl methyl cellulose phthalate, the co-precipitation medium is suitably a weakly acidic medium (pH in the range of 0.5 to 5.0, typically 0.8 to 2.0), typically 0.5N hydrochloric acid or acetic acid;

30 (b) in the case where the carrier or excipient is an acid soluble polymethylacrylate, the co-precipitation medium is suitably a neutral or basic medium, (pH in the range 6.0 to 13.0), water or dilute alkali being appropriate representatives of suitable co-precipitation media; and

35 (c) in the case where the carrier or excipient is hydroxypropylcellulose, an appropriate co-precipitation medium is again water, aptly with a temperature of greater than about 40°C, such as 70 to 80°C.

The synthesis of Compound A and of intermediates useful in the preparation thereof, are illustrated by the following, non-limiting Examples.

Intermediate 1

5 (R)-N⁸-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

To a suspension of D-tryptophan methyl ester hydrochloride (10.2g) in anhydrous CH₂Cl₂ (150ml) cooled at 0°C was added dropwise triethylamine (12.3ml). To the resulting solution solid piperonyl chloride (8.16g) was added portionwise at the same temperature, and the mixture was stirred at room temperature for 2 hours. The mixture was washed successively with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of NaHCO₃ and again with water. After drying over Na₂SO₄ and evaporation of the solvent under reduced pressure, the resulting oil on trituration from hot cyclohexane afforded the title compound as a white solid (14.7g).

15

mp : 123-124°C

20°

[α]_D = -84.4° (c = 1.04, CHCl₃).

20

Intermediate 2

(R)-N⁸-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

A mixture of Intermediate 1 (14g) and Lawesson's reagent (9.28g) in dimethoxyethane (280ml) was heated at 60°C under N₂ for 16 hours with stirring. The reaction mixture was evaporated to dryness and the resulting oil was dissolved in ethyl acetate, then washed successively with an aqueous saturated solution of NaHCO₃ and water and dried over Na₂SO₄. The oily residue obtained after evaporation under reduced pressure gave, on trituration from cyclohexane, a yellow powder which was filtered and washed with cooled methanol to afford the title compound (9.74g).

25

mp : 129-130°C

20°

[α]_D = -166.8° (c = 1.14, CHCl₃).

30

Intermediate 3

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of Intermediate 2 (9g) and methyl iodide (10ml) in anhydrous dichloromethane (200ml) was heated at reflux under an argon atmosphere with protection from light. After 24 hours, the solvent was removed under reduced pressure to give an orange oil which on trituration from hexane gave a solid which was washed with ether and used without further purification in the next step. This compound (13.11g) was dissolved in methanol (250ml) and the solution was cooled to -78°C. NaBH₄ (0.99g) was then added by portions and the mixture was stirred at the same temperature for 1 hour. The reaction was quenched by addition of acetone (10ml) and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water and then with brine and dried over Na₂SO₄. After evaporation of the solvent, the orange oil gave on trituration from a hot mixture of diethyl ether/cyclohexane an orange powder which was recrystallised from diethyl ether/pentane to afford the title compound as a pale yellow solid (5.15g).

mp: 154 - 155°C

20°

[α]_D²⁰ = +24.4° (c = 1.03, CHCl₃).

Intermediate 4

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

To a stirred solution of Intermediate 3 (9.7g) and NaHCO₃ (2.79g) in anhydrous CHCl₃ (200ml) was added dropwise chloroacetyl chloride (5.3ml) at 0°C under N₂. The resulting mixture was stirred for 1 hour at the same temperature and diluted with CHCl₃ (100ml). Water (100ml) was then added dropwise with stirring to the mixture, followed by a saturated aqueous solution of NaHCO₃. The organic layer was washed with water until neutrality and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, the oily compound obtained was crystallised from ether to give the title compound as a pale yellow solid (9.95g).

mp : 233°C

126 122

14

20°
[α]_D = - 125.4° (c = 1.17, CHCl₃).

Method B

5 Chloroacetyl chloride (4ml) was added dropwise to a solution of Intermediate 3 (16.1g) and triethylamine (7ml) in anhydrous CH₂Cl₂ (200ml) at 0°C under N₂. The solution was stirred at 0°C for 30 minutes, then diluted with CH₂Cl₂ (300ml). The solution was washed with water (200ml), a saturated aqueous solution of NaHCO₃ (300ml) and brine (400ml). After drying over Na₂SO₄ and
10 evaporation under reduced pressure, the resulting solid was washed with ether (300ml) to give the title compound as a pale yellow solid (18.3g).

Example 1:

15 (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2,1-b:3,1'-b']pyrido[3,4-b]indole-1,4-dione (Compound A)
To a stirred suspension of Intermediate 4 (12.5g) in MeOH (400ml) was added at room temperature a solution of methylamine (33% in EtOH) (13.7ml) and the resulting mixture was heated at 50°C under N₂ for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (1l).
20 After washing with water (3 x 500ml), drying over Na₂SO₄ and evaporating to dryness, the white solid obtained was recrystallised from 2-propanol to give the title compound as white needles (7.5g).

mp : 298-300°C.

20°
25 [α]_D = + 71.3° (c = 0.55, CHCl₃).

Elemental analysis (C₂₂H₁₉N₃O₄) calculated: C, 67.86; H, 4.82; N, 10.79;
found: C, 67.79; H, 4.95; N, 10.61%.

30 Co-precipitation of Compound A: Hydroxypropyl methylcellulose phthalate using acetone/water

	%
Compound A	25 - 60
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75
35 * Grades HP55 and HP50.	

15

Compound A (1g) and HPMCP (1g) were dissolved in a 9:1 mixture of acetone/water (27 ml). 0.25M Hydrochloric acid (83ml) was added. The resultant co-precipitate was filtered, washed with water (5x 3ml), dried in vacuo and milled.

5

Co-precipitation of Compound A: Hydroxypropyl methylcellulose phthalate using tetrahydrofuran/water

	%
Compound A	25 - 90
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75
* Grades HP55 and HP50.	

10

Compound A (1g) and HPMCP (1g) were dissolved in a 9:1 mixture of tetrahydrofuran/water (10ml) and the resultant solution was added to a solution of glacial acetic acid (2.25ml) in water (37.7ml). The resultant precipitate was filtered, washed with water (5x3ml), dried in vacuo and milled.

15

Co-precipitation of Compound B: Hydroxypropyl methylcellulose phthalate using acetone/methanol

	%
Compound B	25 - 90
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75
* Grades HP55 and HP50.	

20

Compound B (0.65g) and HPMCP (0.65g) were dissolved in a 1:1 mixture of acetone and methanol (35ml). 0.5N Hydrochloric acid (50ml) was added followed by distilled water (50ml). The resultant precipitate was collected, washed with aqueous hydrochloric acid, filtered, and dried in vacuo.

25

30

TABLETS FOR ORAL ADMINISTRATION

Co-precipitates of Compound A: HPMCP and Compound B: HPMCP were formulated as follows:

35

128 124

16

Compound A: HPMCP co-precipitate was blended with the excipients. The resultant mix was compressed into tablets.

1.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	289.2
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

2.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	229.2
Lactose (anhydrous)	52.0
Colloidal silicon dioxide	0.8
Crospovidone	16.0
Magnesium stearate	2.0

5

3.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	249.2
Polyvinyl pyrrolidone	40.0
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

4.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	281.2
Sodium lauryl sulphate	8.0
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

12A 12S

5.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	61.87
Dibasic calcium phosphate anhydrous	62.00
Croscarmellose Sodium	10.00
Sodium lauryl sulphate	5.0
Polyvidone 30	9.38
Colloidal silicon dioxide	0.5
Magnesium stearate	1.25

Compound B: HPMCP co-precipitate was blended with the excipients. The resultant mix was compressed into tablets.

5

1.	mg/tablet
Compound B: HPMCP co-precipitate	10.0
Microcrystalline cellulose	66.74
Dibasic calcium phosphate anhydrous	66.74
Croscarmellose sodium	6.00
Magnesium stearate	0.53

Tablets of other strengths may be prepared by altering the ratio of Compound A or B: HPMCP co-precipitate to the other excipients.

10 **FILM COATED TABLETS**

The aforementioned tablet formulations were film coated.

Coating Suspension	% w/w
Opadry white +	13.2
Purified water	to 100.0*

15 * The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20mg/tablet.

(b) co-precipitating the compound and the carrier or excipient.

5 16. A process as claimed in Claim 15 wherein the carrier or excipient is hydroxypropyl methyl cellulose phthalate.

10 17. A process as claimed in Claim 15 or Claim 16, wherein the co-precipitation medium is a weakly acidic medium selected from hydrochloric acid and acetic acid.

18. A process as claimed in any one of Claims 15-17, wherein the solvent employed is selected from acetone and tetrahydrofuran, in a mixture comprising a 10% ratio of water.

15 19. A process of preparing a solid dispersion comprising (+)-N-[1-(adamantanemethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodisazepin-3-yl]-N'-phenylurea or salts or solvates thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

20 (a) providing an intimate mixture of a poorly water soluble drug selected from Compound A or Compound B, the carrier or excipient therefor and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water; and

25 (b) co-precipitating the compound and the carrier or excipient.

30 20. A process as claimed in Claim 19 wherein the carrier or excipient is hydroxypropyl methyl cellulose phthalate.

21. A process as claimed in Claim 19 or Claim 20, wherein the acidic medium is 0.5N hydrochloric acid.

35 22. A process as claimed in any one of Claims 19-21, wherein the solvent employed is a combination of acetone and methanol.

23. A solid dispersion consisting of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':8,1]pyrido[3,4-b]indole-1,4-dione and a pharmaceutically acceptable carrier or excipient therefor. }

5

24. A solid dispersion as claimed in Claim 23 for use in therapy.

10

25. A solid dispersion as claimed in Claim 23 for use in the manufacture of a medicament for the treatment of conditions where inhibition of PDEV is of therapeutic benefit.

15

26. A method of treating in conditions where inhibition of PDEV is of therapeutic benefit in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a solid dispersion as claimed in Claim 23.

20

27. A solid dispersion consisting of (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea and a pharmaceutically acceptable carrier or excipient therefor.

25

28. A solid dispersion as claimed in Claim 27 for use in therapy.

29. The use of a solid dispersion as claimed in Claim 27 for the manufacture of a medicament for the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit.

30

30. A method for the treatment of a mammal, including man, in particular in the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit which method comprises administering to the patient an effective amount of a solid dispersion as claimed in Claim 27.

35

31. A pharmaceutical composition comprising a solid dispersion as claimed in Claim 23 or Claim 24, together with a pharmaceutically acceptable carrier therefor.

United States Patent [19]

Daugan

[11] Patent Number: 5,859,006
[45] Date of Patent: Jan. 12, 1999

[54] TETRACYCLIC DERIVATIVES; PROCESS OF PREPARATION AND USE

[75] Inventor: Alain Claude-Marie Daugan, Les Ulis, France

[73] Assignee: ICOS Corporation, Bothell, Wash.

[21] Appl. No.: 669,389

[22] PCT Filed: Jan. 19, 1995

[86] PCT No.: PCT/EP95/00183

§ 371 Date: Jul. 17, 1996

§ 102(e) Date: Jul. 17, 1996

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PCT Pub. Date: Jul. 27, 1995

[30] Foreign Application Priority Data

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[51] Int. Cl.⁶ A01N 43/58; A01N 43/42; C07D 241/36; C07D 471/00

[52] U.S. Cl. 514/249; 514/250; 514/292; 544/343; 546/81; 546/85

[58] Field of Search 544/343; 514/249, 514/250, 292; 546/81, 85

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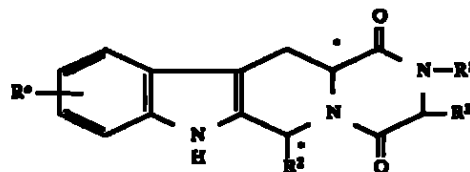
Primary Examiner—Mukund J. Shah

Assistant Examiner—Thumthom T. Ngo

Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein, Murray & Boran

[57] ABSTRACT

A compound of formula (I)



and salts and solvates thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;

R¹ represents hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl; R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R³ represents hydrogen or C₁₋₃alkyl, or R¹ and R³ together represent a 3- or 4-membered alkyl or alkenyl chain.

A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders.

15 Claims, No Drawings

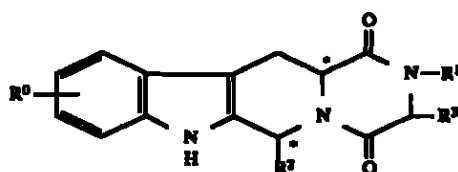
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TETRACYCLIC DERIVATIVES; PROCESS OF PREPARATION AND USE

This is a 371 application of Pct/EP filed on Jan. 19, 1995.

This invention relates to a series of tetracyclic derivatives, to processes for their preparation, pharmaceutical compositions containing them, and their use as therapeutic agents. In particular, the invention relates to tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders.

Thus, according to a first aspect, the present invention provides compounds of formula (I)



and salts and solvates (e.g. hydrates) thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;

R¹ represents hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl;

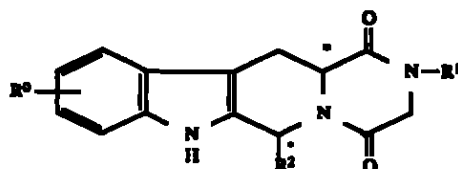
R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R² represents hydrogen or C₁₋₆alkyl, or R¹ and R² together represent a 3- or 4- membered alkyl or alkenyl chain.

There is further provided by the present invention a subgroup of compounds of formula (I), the subgroup comprising compounds of formula (Ia)



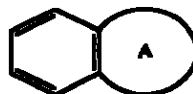
and salts and solvates (e.g. hydrates) thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;

R¹ represents hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl; and

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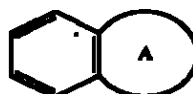
R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



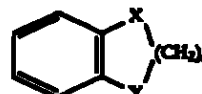
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

Within R¹ above, the term "aryl" as part of an arylC₁₋₃alkyl group means phenyl or phenyl substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy and methylenedioxy. The term "heteroaryl" as part of a heteroarylC₁₋₃alkyl group means thienyl, furyl or pyridyl each optionally substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C₁₋₆alkyl and C₁₋₆alkoxy. The term "C₃₋₆cycloalkyl" as a group or part of a C₃₋₆cycloalkylC₁₋₃alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C₃₋₆cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within R² above, optional benzene ring substituents are selected from one or more (e.g. 1; 2 or 3) atoms or groups comprising halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, —CO₂R^b, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, cyano, nitro and NR^aR^b, where R^a and R^b are each hydrogen or C₁₋₆alkyl, or R^a may also represent C₂₋₆alkanoyl or C₁₋₆alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, C₁₋₆alkyl, C₁₋₆alkoxy and arylC₁₋₃alkyl as defined above. The bicyclic ring



may, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene or benzofuran or



(where n is an integer 1 or 2 and X and Y may each represent CH₂, O, S or NH).

In the above definitions, the term "alkyl" as a group or part of a group means a straight chain or, where available, a branched chain alkyl moiety. For example, it may represent a C₁₋₆alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. The term "alkenyl" as used herein includes straight-chained and branched alkenyl groups, such as vinyl and allyl, groups. The term "alkynyl" as used herein includes straight-chained and branched alkynyl groups, suitably acetylene. The term "halogen" herein means a fluorine, chlorine, bromine or iodine atom. The term "haloC₁₋₆alkyl" means an alkyl group

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

A specific compound of the invention is: (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where inhibition of cGMP specific PDE is thought to be beneficial.

As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic, vasodilatory, natriuretic and diuretic activities as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF), nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT₁. The compounds of formula (I) therefore have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome).

It will be appreciated that references herein to treatment extend to prophylaxis as well as treatment of established conditions.

It will also be appreciated that 'a compound of formula (I)', or a physiologically acceptable salt or solvate thereof can be administered as the raw compound, or as a pharmaceutical composition containing either entity.

There is thus provided as a further aspect of the invention a compound of formula (I) for use in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

According to another aspect of the invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

In a further aspect, the invention provides a method of treating stable, unstable and variant (Prinzmetal) angina,

hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS) in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a compound with formula (I).

Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration. Oral administration is generally preferred.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I) will generally be in the range of from 0.5800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witexol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and capryliccapric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

A compound of formula (I) may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states. The

invention thus provides, in another aspect, a combination of a compound of formula (I) together with another therapeutically active agent.

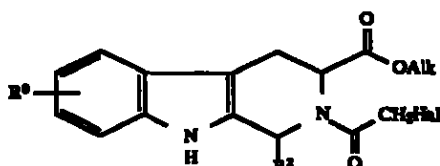
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a compound of formula (I) will be readily appreciated by those skilled in the art.

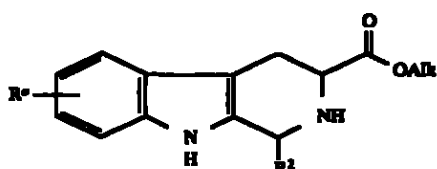
Compounds of formula (I) may be prepared by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below R^0 , R^1 and R^2 are as defined in formula (I) above unless otherwise indicated.

Thus, a process (A) for preparing a compound of formula (I) wherein R^3 represents hydrogen comprises treating a compound of formula (II)



(in which Alk represents C_{1-6} alkyl, e.g. methyl or ethyl and Hal is a halogen atom, e.g. chlorine) with a primary amine R^1NH_2 in a suitable solvent such as an alcohol (e.g. methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from $20^\circ C.$ to reflux (e.g. at about $50^\circ C.$).

A compound of formula (II) may conveniently be prepared by treating a compound of formula (III)



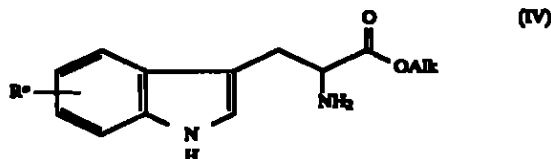
with a haloacetyl halide (e.g. chloroacetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). The reaction may conveniently be effected at a temperature of from $-20^\circ C.$ to $+20^\circ C.$ (e.g. at about $0^\circ C.$).

A compound of formula (I) may also be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) may be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g. racemates) of either pairs of cis or trans isomers from the corresponding mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC (high performance liquid chromatography) on a chiral column such as Hyperall naphthylurea.

A compound of formula (III) may conveniently be prepared from a tryptophan alkyl ester of formula (IV)



(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) according to either of the following procedures (a) and (b). Procedure (b) is only suitable for preparing cis isomers of formula (III) and may be particularly suitable for preparing individual cis enantiomers of formula (III) from D- or L-tryptophan alkyl esters as appropriate.

Procedure (a)

This comprises a Pictet-Spengler cyclisation between a compound of formula (IV) and an aldehyde R^2CHO . The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from $-20^\circ C.$ to reflux to provide a compound of formula (III) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which may be either individual enantiomers or racemates of pairs of cis or trans isomers depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers may conveniently be separated from mixtures thereof by fractional crystallisation or by chromatography (e.g. flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers may be separated by chromatography (e.g. flash column chromatography) using appropriate eluents. An optically pure trans isomer may also be converted to an optically pure cis isomer using suitable epimerisation procedures. One such procedure comprises treating the trans isomer or a mixture (e.g. 1:1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from $0^\circ C.$ to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilising aqueous hydrogen chloride the desired cis isomer precipitates out as the hydrochloride salt which may then be isolated by filtration.

Procedure (b)

This comprises a four-step procedure from a compound of formula (IV) or a salt thereof (e.g. the hydrochloride salt). The procedure is particularly suitable for preparing a 1R, 3R isomer of formula (III) from a D-tryptophan alkyl ester of formula (IV) or a salt thereof (e.g. the hydrochloride salt). Thus, a first step (i) comprises treating a compound of formula (IV) with an acid halide R^2COHal (where Hal is as previously defined) in the presence of a base, e.g. an organic base such as a trialkylamine (for example triethylamine), to provide a compound of formula (V)

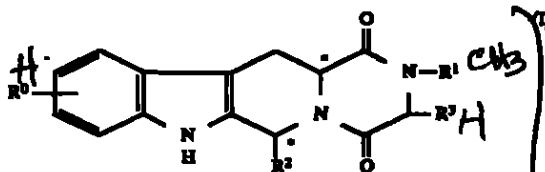
table 2 were studied in conscious spontaneously hypertensive rats (SHR). The compounds were administered orally at a dose of 5 mg/kg in a mixture of 5% DMF and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. The results are expressed as Area Under the Curve (AUC from 0 to 5 hours, mmHg.hour) of the fall in blood pressure over time.

In Vivo results

Example No.	AUC PO (mmHg.h)
36	99
63	95
79	171
82	111
84	77
89	117
95	135
101	136

I claim:

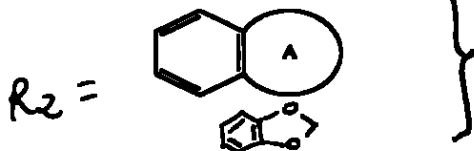
1. A compound of formula (I)



or salts or solvates thereof, in which:

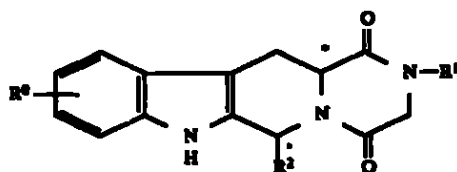
R^0 represents hydrogen, halogen or C_{1-6} alkyl;
 R^1 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl, wherein aryl is phenyl or phenyl substituted with one to three substituents selected from the Group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, methylenedioxy, and mixtures thereof, or heteroaryl C_{1-3} alkyl, wherein heteroaryl is thienyl, furyl, or pyridyl, each optionally substituted with one to three substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, and mixtures thereof;

R^2 represents an optionally substituted mono-cyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



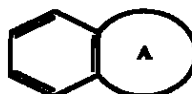
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and R^3 represents hydrogen or C_{1-3} alkyl, or R^1 or R^3 together represent a 3- or 4-membered alkyl or alkenyl chain component of a 5- or 6-membered ring.

2. A compound of formula (Ia)



or salts or solvates thereof, in which:

R^0 represents hydrogen, halogen or C_{1-6} alkyl;
 R^1 represents hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl or heteroaryl C_{1-3} alkyl; and
 R^2 represents an optionally substituted mono-cyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

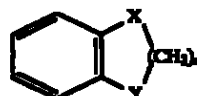
3. A compound according to claim 1, wherein R^0 represents hydrogen.

4. A compound according to any of claim 1, wherein R^1 represents hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl, pyridyl C_{1-3} alkyl, furyl C_{1-3} alkyl or optionally substituted benzyl.

5. A compound according to claim 1, wherein R^1 and R^3 together represent a 3-membered alkyl chain.

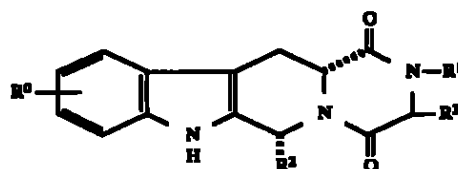
6. A compound according to claim 1, to wherein R^3 represents hydrogen.

7. A compound according to claim 1, wherein R^2 represents an optionally substituted benzene, thiophene, furan, pyridine or naphthalene



where n is ring or an optionally substituted bicyclic ring 1 or 2 and X and Y are each CH_2 or O.

8. A cis isomer of formula (I) represented by formula (Ib)



and mixtures thereof with its cis optical enantiomer, including racemic mixtures, or salts or solvates of these compounds in which R^0 is hydrogen or halogen and R^1 , R^2 and R^3 are as defined in claim 1.

9. A method of treating stable, unstable and variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood

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vessel patency, peripheral vascular disease, vascular disorders, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a human or non-human animal body, which method comprises administering to said body a therapeutically effective amount of a compound according claim 1.

10. A pharmaceutical composition comprising a compound of the according claim 1, together with a pharmaceutically acceptable diluent or carrier therefor.

11. A process of preparing a pharmaceutical composition comprising a compound according to claim 1, which process comprises mixing said compound together with a pharmaceutically acceptable diluent or carrier therefor.

12. *Cis*-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

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(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-[3,4]-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

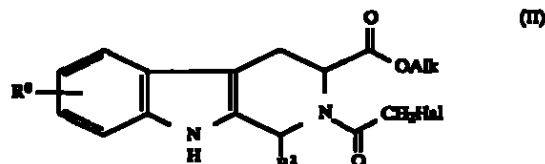
(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

or physiologically acceptable salts or solvates thereof.

13. (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

or physiologically acceptable salts or solvates thereof.

14. A process of preparing a compound of formula (I), wherein R³ represents hydrogen, which process comprises treating a compound of formula (II)



in which Alk represents C₁₋₆ alkyl and Hal is a halogen atom, with a primary amine R₁NH₂ or the process as hereinbefore described followed by

- i) an interconversion step; and/or either
- ii) salt formation; or
- iii) solvate formation.

15. Compounds of formulas (II).

* * * * *

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P-354

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020

Bogotá, D.C., Noviembre 21 de 2005

Doctora

DILIA RODRÍGUEZ D'ALEMÁN

ASUNTO

Radicación No.

00 058 158

Trámite

002

Evento

001

Actuación

430 1 1 2 6 4

Oficio No.

Folios

0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

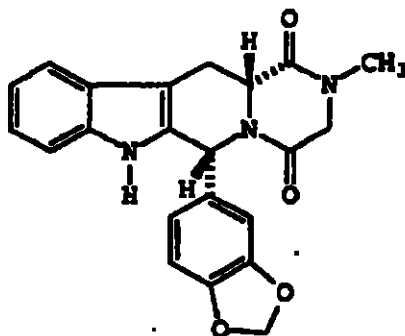
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 4 - 33 y el nuevo capítulo reivindicatorio de los folios 92 - 98 de la solicitud en estudio.

2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 4 se refieren a una forma en partículas de un compuesto de fórmula:



(6R, 12aR)-2,3,6,7,12,12^a-hexahidro-2-metil-6-(3,4-metilendioxfenil)pirazino[2',1':6,1]pirido[3,4-b]indol-1,4-diona

donde el 90 % de las partículas es menor que 40, 25, 15 ó 10 micras.

Las reivindicaciones 5 - 6, 12, 13, 16 se refieren a una composición

farmacéutica que contiene la forma en partículas de la droga de la reivindicación 1.

Las reivindicaciones 7 - 9 se refieren a un método para tratamiento que consiste en administrar un compuesto.

Las reivindicaciones 10 - 11 se refieren a una composición farmacéutica que contiene la forma en partículas de la droga de la reivindicación 1, que logra una $C_{máx}$ de 180 - 280 microgramos/lit.

Las reivindicaciones 14 y 15 se refieren a un método para manufacturar la forma en partículas de la droga de la reivindicación 1 que comprende: (a) proveer el compuesto y (b) reducir el tamaño de partículas para que el 90 % de las partículas sea menor que 40 micras y (c) mezclarlas con excipientes farmacéuticamente aceptables.

Las reivindicaciones 17 y 18 se refieren al uso de partículas de la droga de la reivindicación 1.

La reivindicación 19 se refiere a "la invención como se ha descrito".

El problema planteado en esta solicitud es la necesidad de proporcionar una formulación uniforme y estable de beta-carbolina con buena disponibilidad.

Para resolver este problema técnico la solicitud en estudio proporciona partículas de la droga de la reivindicación 1.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/4985 // 31/395.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 147 048 de Agosto 3 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Las reivindicaciones 7 - 9 se refieren al método para tratamiento que consiste en administrar un compuesto.

Se observa que el método de tratamiento que comprende administrar una composición, de las reivindicaciones 7 -9, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método de tratamiento que comprende administrar una composición, de las reivindicaciones 7 - 9, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

4. Usos

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el artículo 16 de la presente Decisión, no serán objeto de*

nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial".

Se aclara que los usos reivindicados del compuesto no pueden ser objeto de nueva patente, aunque el solicitante los considere distintos a los originalmente comprendidos por la patente inicial, porque estos se conocían originalmente en la Pat US 5 859 006 (ver columna 5), donde se enseñan las indicaciones terapéuticas del compuesto reivindicado en la solicitud en estudio.

5. Claridad de la Solicitud

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a las reivindicaciones 10 - 11 se observa que estas no definen la composición farmacéutica porque mencionan un valor de Cmax, lo cual no la caracteriza. Se recuerda que el resultado a alcanzar no es una característica técnica de la invención. Las reivindicaciones deben definir la invención por sus características esenciales y no por el resultado a alcanzar (tal como la Cmax), puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Debe hacerse la corrección necesaria.

En cuanto a la reivindicación 19 que se refiere a "la invención como se ha descrito", se observa que no define en lo que consiste el objeto de la solicitud. Se sugiere retirar esta reivindicación, que por ser tan general, no define el objeto de la solicitud.

6. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es Agosto 3 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	GB 2 293 103	Composiciones de modafinil de tamaño de partícula definido	Mar 20, 1996
D2	WO 98 38131	Método de producir una dispersión sólida de una droga poco soluble	Dic 5, 1996

		en agua	
D3	US 5 859 008	Derivados tetracíclicos; proceso de preparación y uso	Ene 12, 1999

7. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

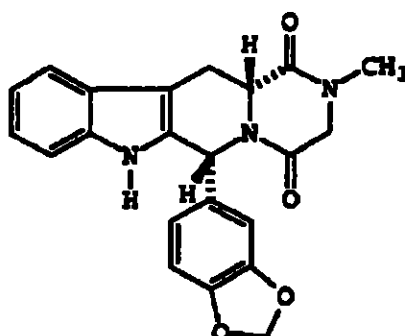
Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."*

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida.

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40".

Las reivindicaciones 1 – 4 se refieren a una forma en partículas de un compuesto de fórmula:



(6R, 12aR)-2,3,6,7,12,12^a-hexahidro-2-metil-6-(3,4-metilendioxifenil)pirazino[2',1':8,1]pírido[3,4-b]índol-1,4-diona

donde el 90 % de las partículas es menor que 40, 25, 15 ó 10 micras.

Las reivindicaciones 5 – 6, 12, 13, 16 se refieren a una composición farmacéutica que contiene la forma en partículas de la droga de la reivindicación 1.

Las reivindicaciones 14 y 15 se refieren a un método para manufacturar la forma en partículas de la droga de la reivindicación 1 que comprende: (a) proveer el compuesto y (b) reducir el tamaño de partículas para que el 90 % de las partículas sea menor que 40 micras y (c) mezclarlas con excipientes farmacéuticamente aceptables.

D1 enseña principios activos de tamaño de partícula de 2 – 60 micras. Además enseña que el tamaño de partícula afecta la velocidad de disolución y la concentración en plasma. Y aclara que los métodos de disminución de tamaño de partícula por molienda y cribado son bien conocidos en la técnica.

D2 enseña el compuesto (6R, 12aR)-2,3,6,7,12,12^a-hexahidro-2-metil-6-(3,4-metilendioxfenil)pirazino[2',1':6,1]pirido[3,4-b]indol-1,4-diona y sus sales y las composiciones que lo contienen, conformadas con un excipiente farmacéuticamente aceptable.

D3 enseña el compuesto (6R, 12aR)-2,3,6,7,12,12^a-hexahidro-2-metil-6-(3,4-metilendioxfenil)pirazino[2',1':6,1]pirido[3,4-b]indol-1,4-diona y sus sales y las composiciones que lo contienen, conformadas con un excipiente farmacéuticamente aceptable. También enseña su uso para la manufactura de medicamentos y con fines terapéuticos (ver columna 5).

Se observa que el compuesto reivindicado no es nuevo. No es nuevo el rango de tamaño de partícula reivindicado. No son nuevas las composiciones que lo contienen. Ni el método de manufactura que consiste en reducir las partículas a un tamaño menor que 40 micras y mezclarlas con excipientes farmacéuticamente aceptables.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Se observa que las anterioridades sugieren el compuesto, el rango de tamaño de partícula, las composiciones que lo contienen y el método de manufactura que consiste en reducir las partículas a un tamaño menor que 40 micras y mezclarlas con excipientes farmacéuticamente aceptables, que son objeto de esta solicitud, por lo cual no hay nivel inventivo.

Debido a que: (a) el compuesto que caracteriza a las composiciones de esta solicitud era conocido en las anterioridades, para una persona conocedora de la materia era evidente el elaborar las composiciones de manera similar; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial al compuesto ni a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvias para una persona versada en la materia y (c) el problema planteado en esta solicitud que era la necesidad de proporcionar necesidad de proporcionar una formulación uniforme y estable de beta-carbolina con buena disponibilidad se resuelve proporcionando partículas de (6R, 12aR)-2,3,6,7,12,12^a-hexahidro-2-metil-6-(3,4-metilendioxfenil)pirazino[2',1':6,1]pirido[3,4-b]indol-1,4-diona, donde el 90 % de las partículas es menor que 40, 25, 15 ó 10 micras, es decir de manera similar a como se resolvía en las anterioridades; las reivindicaciones son obvias y evidentes para una persona versada en la materia. De manera que no tienen nivel inventivo.

8. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

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Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	GB 2 293 103	1 - 19	Novedad y Nivel inventivo
D2	WO 96 38131	1 - 19	Novedad y Nivel inventivo
D3	US 5 859 006	1 - 19	Novedad y Nivel inventivo

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



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

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

El anterior requerimiento fue notificado por fijación en lista, de fecha
01 DIC 2005

CONCEPTO TÉCNICO No. 1864	EXAMINADOR TÉCNICO Código 202007
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