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PATENTE DE INVENCION

05-9445

21. EXPEDIENTE No.

54. TITULO Polimorfo Nuevos del N-Metil-N(3-{3-E2-
-f-enitenduril}-pirazol-[-1,5a]-Pirimidina-7-yl}fenil)

51. CLASIFICACION INTERNACIONAL C07D 487/04

A61K31/519; A61P25/00.

71. SOLICITANTE Novartis Biosciences, Inc.

DOMICILIO San Diego, California, USA.

74. APODERADO Delia Maria Rodriguez D' Aleman

22. BOGOTA, D.C., Feb. 1/2005.

(SS)

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1) SOLICITUD DE:

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☐ Patente de Modelo de Utilidad

☐ Capítulo I.

☒ Capítulo II.

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6) Título (54) POLIMORFO NOVEDOSO DEL N-METIL-N-(3-{3-[2-TIENILCARBONIL]-
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Y COMPUESTOS Y MÉTODOS RELACIONADOS

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***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
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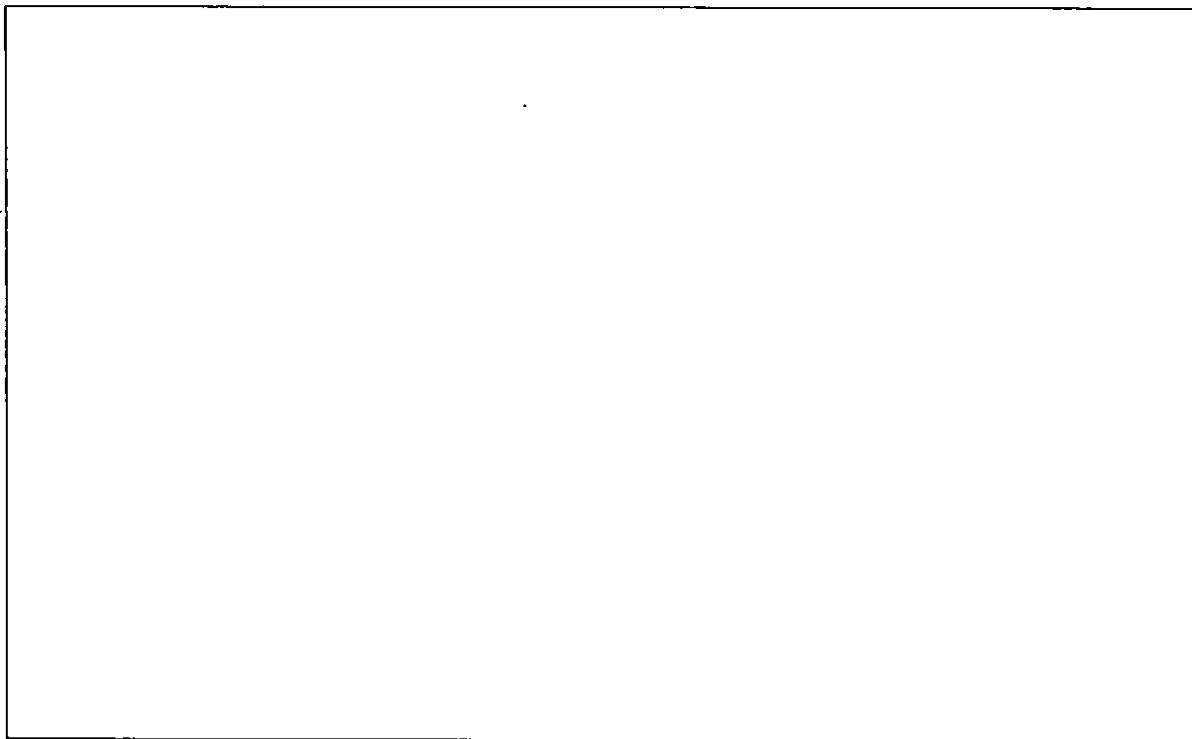
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10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 - 1. Reporte internacional de búsqueda
 - 2. Búsqueda Internacional US 2002/0107256 A1

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL POLYMORPH OF N-METHYL-N-(3-{3-[2-THIENYL-CARBONYL]-PYRAZOL-[1,5-ALPHA]-PYRIM-
IDIN-7-YL}PHENYL)ACETAMIDE AND COMPOSITIONS AND METHODS RELATED THERETO

(57) Abstract: Polymorph Form III of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5-a]-pyrimidin-7-yl}phenyl)acetamide,
and use thereof as a sedative-hypnotic, anxiolytic, anticonvulsant, and/or skeletal muscle relaxant agent. Related compositions and
methods are also disclosed, particularly with regard to treatment of insomnia.

WO 2004/018476 A1

NOVEL POLYMORPH OF N-METHYL-N-(3-{3-[2-THIENYLCARBONYL]-
PYRAZOL-[1,5- α]-PYRIMIDIN-7-YL}PHENYL)ACETAMIDE
AND COMPOSITIONS AND METHODS RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims the benefit of U.S. Provisional Application No. 60/406,072 filed August 26, 2002, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

10 This invention is generally directed to a novel polymorph of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide which has activity over a wide range of indications, and is particularly useful for the treatment of insomnia, and to related processes, compositions and methods.

Description of the Related Art

15 The term "insomnia" is used to describe all conditions related to the perception of inadequate or non-restful sleep by the patient (Dement, *International Pharmacopsychiatry* 17:3-38, 1982). If left untreated, insomnia may result in disturbances in metabolism and overall body function including reduced productivity and significant changes in mood, behavior and psychomotor function, and a higher
20 incidence of morbidity and mortality.

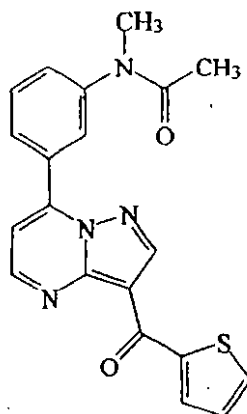
 Traditionally, the management of insomnia includes treatment and/or mitigation of the etiological factors, improving sleep hygiene and the administration of hypnotic agents. The early hypnotic agents, such as barbiturates, while effective, elicited a spectrum of unwanted side effects and longer-term complications. For
25 example, barbiturates have the potential to result in lethargy, confusion, depression and a variety of other residual effects many hours post dosing, as well as having a potential for being highly addictive.

During the 1980's, the pharmaceutical treatment of insomnia shifted away from barbiturates and other CNS depressants toward the benzodiazepine class of sedative-hypnotics. This class of sedative-hypnotic agents showed substantial effectiveness in producing a calming effect which results in sleep-like states in man and
5 animals (Gee et al., *Drugs in Central Nervous Systems*, Horwell (ed.), New York, Marcel Dekker, Inc., 1985, p. 123-147) and had a greater safety margin than prior hypnotics, barbiturates or chloral hydrate (Cook and Sepinwall, *Mechanism of Action of Benzodiazepines*, Costa and Greengard (eds.), New York, Raven Press, 1975, p. 1-28). As with barbiturates, however, many benzodiazepines also possess side effects
10 that limit their usefulness in certain patient populations. These problems include synergy with other CNS depressants (especially alcohol), the development of tolerance upon repeat dosing, rebound insomnia following discontinuation of dosing, hangover effects the next day, and impairment of psychomotor performance.

More recently, a new class of agents has undergone development. These
15 agents are non-benzodiazepine compounds, which bind selectively to a specific receptor subtype of the benzodiazepine receptor. This receptor selectivity is thought to be the mechanism by which these compounds are able to exert a robust hypnotic effect, while also demonstrating an improved safety profile relative to the non-selective, benzodiazepine class of agents. The first of these agents to be approved by the United
20 States Food and Drug Administration (FDA) for marketing in the United States was Ambien (zolpidem tartrate), which is based on the imidazopyridine backbone (*see* U.S. Patent Nos. 4,382,938 and 4,460,592). In addition to Ambien, another compound known as Sonata (zaleplon), which is a pyrazolopyrimidine-based compound, has received FDA approval (*see* U.S. Patent No. 4,626,538). Other non-benzodiazepine
25 compounds and/or methods for making or using the same have also been reported (*see, e.g.,* 4,794,185, 4,808,594, 4,847,256, 5,714,607, 4,654,347; 5,891,891).

While significant advances have been made in this field, there is still a need in the art for compounds that are effective as sedative or hypnotic agents generally, particularly in the context of treating insomnia. One such compound is N-methyl-N-(3-
30 {3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide (referred to

herein as "Compound 1"). Compound 1 is disclosed in U.S. Patent No. 6,399,621 and has the following chemical structure:



Compound 1

In addition, U.S. Patent Nos. 6,384,221 and 6,544,999 are directed to polymorph Form I and Form II of Compound 1, while U.S. Patent Nos. 6,472,528 and 6,485,746 are directed to synthesis and controlled release, respectively, of Compound 1.

While Compound 1 has proven particularly promising for the treatment of insomnia, improved forms of this compound are desired, particularly with regard to enhanced solubility, oral bioavailability, ability to be readily formulated, ease of synthesis, and/or physical stability. The present invention fulfills one or more of these needs and provides further related advantages.

BRIEF SUMMARY OF THE INVENTION

The present invention is generally directed to a novel polymorphic form of Compound 1, referred to herein as "polymorph Form III". Polymorph Form III exhibits a predominant endotherm peak at about 191°C (as measured by a TA 2920 Modulated Differential Scanning Calorimeter (DSC) at a scan rate of 10°C per minute). Polymorph Form III also exhibits an X-ray Powder Diffraction pattern with characteristic peaks (expressed in degrees 2θ ($\pm 0.2^\circ$)) at one or more of the following positions: 10.2, 13.3, 18.9, 20.7, 22.2, 28.1 and 30.8. More specifically, such characteristic peaks are at 18.9 and 28.1, and further at 10.2, and further at 13.3, 20.7, 22.2 and 30.8.

Polymorph Form III has utility over a wide range of applications, including utility as a sedative and/or hypnotic agent generally and, more specifically, for

the treatment of insomnia. Thus, in another embodiment, methods are disclosed for treating various conditions, including insomnia, by administering an effective amount of polymorph Form III to an animal or subject in need thereof (referred to herein as a "patient"), and typically to a warm-blooded animal (including a human).

5 In one embodiment, polymorph Form III is substantially pure – that is, containing less than 2% by weight total impurities, less than about 1% by weight water, and less than 0.5% by weight residual organic solvent; or, in a more specifically embodiment, less than 1% by weight total impurities, less than about 0.75% by weight water, and less than 0.4% by weight residual organic solvent.

10 In another embodiment, Compound 1 is in the form of a composition or mixture of polymorph Form III along with one or more other crystalline, solvate, amorphous, or other forms of Compound 1. For example, such a composition may comprise polymorph Form III along with one or more other polymorphic forms of Compound 1, such as polymorph Form I and/or Form II. More specifically, the
15 composition may comprise from trace amounts up to 100% polymorph Form III, or any amount in between – for example, the composition may comprise less than 0.1%, 0.5%, 1%, 2%, 5%, 10%, 20%, 30%, 40% or 50% by weight of polymorph Form III based on the total amount of Compound 1 in the composition. Alternatively, the composition may comprise at least 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99%, 99.5% or
20 99.9% by weight of polymorph Form III based on the total amount of Compound 1 in the composition.

Prior to administration, and in further embodiment, polymorph Form III may be formulated as a pharmaceutical composition that contains an effective dosage amount of polymorph Form III in combination with one (or more) pharmaceutically
25 acceptable carrier(s). Such compositions may assume a variety of forms, including pills, tablets and capsules for oral administration.

In still another embodiment, the pharmaceutical composition comprises an effective dosage amount of Compound 1, wherein Compound 1 comprises at least a certain percentage of polymorph Form III (based on the total amount of Compound 1
30 present in the composition – that is, the total amount of Compound 1 being 100%). In other words, at least a certain percentage of Compound 1 present within the

pharmaceutical composition exists as polymorph Form III, with the remainder of Compound 1 being in a different form, including (but not limited to) polymorph Form I, polymorph Form II, or any other crystalline, solvate or amorphous form(s).

In yet a further embodiment, this invention provides processes for making polymorph Form III. For example, polymorph Form III may be made by (a) providing a heated crystallization solvent comprising Compound 1, (b) adding water and a nucleating agent (such as carbon or crystals of polymorph Form III) thereto in amounts sufficient to induce crystallization of polymorph Form III, and (c) collecting crystallized polymorph Form III. Optionally, the crystallization solvent can be cooled after step (b). In an alternative embodiment, polymorph Form III may be made by (a) providing a heated crystallization solvent comprising Compound 1, (b) adding the heated crystallization solvent to a co-solvent or mixture of co-solvents, (c) adding a nucleating agent thereto in amounts sufficient to induce crystallization of polymorph Form III, and (d) collecting crystallized polymorph Form III. Further, polymorph Form III made according to one or more of the processes of this invention is also disclosed.

These and other aspects of this invention will be apparent upon reference to the following detailed description and attached figures. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents is hereby incorporated by reference in its entirety.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Figure 1 is a Differential Scanning Calorimetry (DSC) thermogram of polymorph Form III.

Figure 2 is an X-ray powder diffraction spectrum of polymorph Form III.

Figure 3 is an Raman FT Infrared spectrum of polymorph Form III.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is generally directed to a novel polymorphic form of Compound 1, referred to herein as "polymorph Form III", as well as to compositions containing the same. Also disclosed are methods relating to the

use of polymorph Form III by administration to a patient in need of the same, and to processes for making polymorph Form III.

Solids exist in either amorphous or crystalline forms. In the case of crystalline forms, molecules are positioned in 3-dimensional lattice sites. When a compound recrystallizes from a solution or slurry, it may crystallize with different spatial lattice arrangements, a property referred to as "polymorphism," with the different crystal forms individually being referred to as a "polymorph". Different polymorphic forms of a given substance may differ from each other with respect to one or more physical properties, such as solubility and dissociation, true density, crystal shape, compaction behavior, flow properties, and/or solid state stability. In the case of a chemical substance that exists in two (or more) polymorphic forms, the unstable forms generally convert to the more thermodynamically stable forms at a given temperature after a sufficient period of time. When this transformation is not rapid, the thermodynamically unstable form is referred to as the "metastable" form. In general, the stable form exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. However, the metastable form may exhibit sufficient chemical and physical stability under normal storage conditions to permit its use in a commercial form. In this case, the metastable form, although less stable, may exhibit properties desirable over those of the stable form, such as enhanced solubility or better oral bioavailability.

In the case of Compound 1, two polymorphic forms (*i.e.*, Form I and Form II) have previously been reported (*see* U.S. Patent Nos. 6,384,221 and 6,544,999). Compound 1 is presently undergoing clinical trials for treatment of insomnia. In anticipation of potential large scale production, significant effort has been directed to the commercial-scale production of Compound 1. During one such production run, an impurity was discovered within the end product. In an effort to remove the impurity, carbon was added, followed by recrystallization. As a result of this subsequent work up, it was surprisingly discovered that a new polymorph (*i.e.*, polymorph Form III) was obtained. While not intending to be limited by theory, it is believed that the added carbon served as a nucleation site for formation of polymorph Form III.

9

The novel and surprising polymorph of this invention, polymorph Form III, may be characterized by, for example, melting point and/or X-Ray powder diffraction spectrometry. As shown in Figure 1, polymorph Form III exhibits a predominant endotherm peak at about 191°C as measured by a TA 2920 (TA Instruments, New Castle, Delaware) Modulated Differential Scanning Calorimeter (DSC) at a scan rate of 10°C per minute with an Indium standard. As used herein, the term "about 191°C" means a range of 190 to 192.5°C. In this regard, it should be understood that the endotherm measured by a particular differential scanning calorimeter is dependent upon a number of factors, including the rate of heating (*i.e.*, scan rate), the calibration standard utilized, instrument calibration, relative humidity, and upon the chemical purity of the sample being tested. Thus, an endotherm as measured by DSC on the instrument identified above may vary by as much as $\pm 1^\circ\text{C}$ or even $\pm 1\frac{1}{2}^\circ\text{C}$. Accordingly, the term "about 191°C" is intended to encompass such instrument variations.

The X-Ray powder diffraction spectrum for polymorph Form III is presented in Figure 2, and is set forth in tabular form in Table 1 below. The X-Ray powder diffraction was measured by a Siemens D500 Automated Powder Diffractometer equipped with graphite monochromator and a Cu ($\lambda=1.54$ Angstrom) X-ray source operated at 50kV, 40mA. Two-theta calibration is performed using an NBS mica standard. The sample was analyzed using the following instrument parameters: measuring range = $4-40^\circ 2\theta$; step width = 0.050° ; and measuring time per step = 1.2 sec.

Table 1

X-Ray Powder Diffraction Spectral Lines

<u>d value</u>	<u>$2-\theta^\circ$</u>	<u>Intensity</u>	<u>Intensity %</u>
9.15587	9.652	1388	7.0
8.91589	9.912	7718	39.1
8.65670	10.210	19744	100.0
8.16181	10.831	572	2.9
7.88947	11.206	1398	7.1

6.85166	12.910	765	3.9
6.64840	13.306	4690	23.8
6.29329	14.061	396	2.0
5.24469	16.891	1398	7.1
5.19705	17.047	1731	8.8
5.05094	17.544	1170	5.9
4.76647	18.600	1567	7.9
4.69634	18.880	4865	24.6
4.34978	20.400	1131	5.7
4.29694	20.654	4611	23.4
4.12546	21.522	758	3.8
4.00186	22.195	2281	11.6
3.87889	22.908	1046	5.3
3.72796	23.849	321	1.6
3.56593	24.950	752	3.8
3.51637	25.307	716	3.6
3.40208	26.172	781	4.0
3.34446	26.631	1738	8.8
3.30597	26.947	764	3.9
3.23885	27.516	544	2.8
3.17029	28.124	4022	20.4
3.01819	29.572	480	2.4
2.97878	29.973	264	1.3
2.89811	30.827	2802	14.2
2.79651	31.977	890	4.5
2.77443	32.238	354	1.8
2.60380	34.415	407	2.1
2.53630	35.360	1434	7.3
2.41973	37.124	262	1.3
2.38437	37.695	253	1.3

The crystal structure of polymorph Form III was determined by single crystal X-ray diffraction analysis. A colorless plate of polymorph Form III having dimensions of 0.30 x 0.20 x 0.13 mm was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed with Mo K_{α} radiation ($\lambda = 0.71073 \text{ \AA}$) on a Nonius KappaCCD diffractometer. Data relating to the single crystal X-ray crystallography of polymorph Form III is presented in the following Tables 2-6.

9⁶

Table 2
Crystal Parameters

Space Group	$P2_1/n$
$a, \text{\AA}$	9.5887(3)
$b, \text{\AA}$	10.3985(4)
$c, \text{\AA}$	17.5807(7)
α	90
β	96.8044(14)
γ	90
Z (molecules/unit cell)	4
Calculated Density (g/cm)	1.436
Temperature (K)	150

Table 3
Positional Parameters and Their Estimated Standard Deviations

	Atom	x	y	z	U (Å ²)
5	S(1)	0.46180(7)	-0.27982(8)	0.14578(4)	0.0384(2)
	O(6)	0.62938(19)	-0.0547(2)	0.18402(10)	0.0382(6)
	O(122)	0.8323(3)	0.2180(3)	-0.36178(12)	0.0643(8)
10	N(8)	0.7964(2)	0.1011(2)	0.09047(13)	0.0405(7)
	N(9)	0.8076(2)	0.1723(2)	0.15438(12)	0.0317(6)
	N(14)	0.8428(2)	0.0463(2)	-0.03115(11)	0.0286(6)
	N(12A)	0.9717(5)	0.2278(5)	-0.2546(3)	0.0282(12)
	N(12B)	0.9122(5)	0.3116(5)	-0.2521(3)	0.0319(14)
15	C(2)	0.3830(3)	-0.3736(3)	0.07383(18)	0.0420(9)
	C(3)	0.4087(3)	-0.3309(3)	0.00378(17)	0.0391(8)
	C(4)	0.4960(3)	-0.2230(3)	0.00787(16)	0.0331(7)
	C(5)	0.5358(2)	-0.1829(3)	0.08160(14)	0.0294(7)
	C(6)	0.6305(2)	-0.0805(3)	0.11554(13)	0.0280(7)
20	C(7)	0.7219(2)	-0.0121(2)	0.06857(13)	0.0264(7)
	C(10)	0.8880(3)	0.2745(3)	0.15515(15)	0.0333(7)
	C(11)	0.9616(3)	0.3131(3)	0.09337(14)	0.0311(7)
	C(12)	0.9484(2)	0.2422(3)	0.02666(14)	0.0269(6)
	C(13)	0.8667(2)	0.1337(2)	0.02781(11)	0.0154(5)
25	C(15)	0.7574(3)	-0.0389(3)	-0.00555(14)	0.0289(7)
	C(121)	1.0127(3)	0.2801(2)	-0.04226(14)	0.0272(7)
	C(122)	1.1408(2)	0.3451(2)	-0.03341(14)	0.0278(7)
	C(123)	1.2019(3)	0.3852(3)	-0.09671(14)	0.0292(7)
	C(124)	1.1380(3)	0.3615(3)	-0.17015(16)	0.0412(8)
30	C(125)	1.0100(4)	0.2988(4)	-0.17857(16)	0.0614(11)
	C(126)	0.9462(3)	0.2586(3)	-0.11575(16)	0.0453(8)
	C(12A)	0.8662(6)	0.2827(7)	-0.3016(3)	0.0324(17)
	C(12B)	0.9236(7)	0.2085(7)	-0.2969(4)	0.0361(17)
	C(13A)	1.0305(3)	0.1070(3)	-0.27368(17)	0.0446(9)
35	C(13B)	0.8135(3)	0.4141(3)	-0.27623(17)	0.0430(9)
	H(2)	0.328	-0.447	0.082	0.050
	H(3)	0.371	-0.370	-0.043	0.047
	H(4)	0.525	-0.182	-0.036	0.040
	H(10)	0.898	0.326	0.200	0.040
40	H(11)	1.020	0.387	0.098	0.037
	H(15)	0.723	-0.112	-0.034	0.035
	H(122)	1.186	0.362	0.016	0.033
	H(123)	1.289	0.430	-0.090	0.035
	H(124)	1.181	0.388	-0.214	0.049
45	H(126)	0.857	0.217	-0.123	0.055

50 $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$
Hydrogens included in calculation of structure factors but not refined.

10

Table 4
Anisotropic Temperature Factor Coefficients

5	Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
	S(1)	0.0396(4)	0.0424(5)	0.0333(4)	-0.0081(3)	0.0048(3)	0.0054(3)
	O(6)	0.0505(11)	0.0416(12)	0.0240(10)	-0.0064(9)	0.0105(8)	-0.0006(8)
10	O(122)	0.0705(15)	0.096(2)	0.0248(11)	-0.0246(14)	-0.0014(10)	-0.0111(12)
	N(8)	0.0482(14)	0.0424(15)	0.0313(13)	0.0033(11)	0.0067(10)	0.0017(11)
	N(9)	0.0430(12)	0.0308(13)	0.0220(11)	0.0035(10)	0.0067(9)	-0.0032(9)
	N(14)	0.0346(11)	0.0299(12)	0.0215(10)	-0.0007(9)	0.0039(8)	-0.0037(9)
	N(12A)	0.035(2)	0.035(3)	0.013(2)	0.000(2)	-0.0042(19)	0.0008(19)
15	N(12B)	0.035(2)	0.036(3)	0.024(3)	0.005(2)	0.0010(19)	0.006(2)
	C(2)	0.0354(14)	0.0386(18)	0.0512(19)	-0.0088(12)	0.0014(12)	0.0004(14)
	C(3)	0.0359(15)	0.0408(18)	0.0386(16)	-0.0010(12)	-0.0037(11)	-0.0033(13)
	C(4)	0.0315(13)	0.0382(17)	0.0288(14)	0.0034(11)	-0.0002(10)	-0.0007(12)
	C(5)	0.0295(13)	0.0312(15)	0.0275(13)	0.0042(10)	0.0036(10)	0.0036(11)
20	C(6)	0.0314(13)	0.0292(14)	0.0233(13)	0.0033(10)	0.0030(9)	0.0025(10)
	C(7)	0.0336(13)	0.0252(14)	0.0208(12)	0.0038(10)	0.0043(9)	0.0018(10)
	C(10)	0.0452(15)	0.0324(16)	0.0228(13)	-0.0004(12)	0.0061(11)	-0.0033(11)
	C(11)	0.0396(14)	0.0300(14)	0.0236(12)	-0.0006(11)	0.0038(10)	-0.0019(11)
	C(12)	0.0291(12)	0.0308(14)	0.0208(12)	0.0034(10)	0.0029(9)	0.0023(10)
25	C(13)	0.0207(10)	0.0169(11)	0.0089(9)	0.0014(8)	0.0030(7)	-0.0004(8)
	C(15)	0.0358(13)	0.0282(14)	0.0227(12)	0.0010(10)	0.0031(9)	-0.0011(10)
	C(121)	0.0317(13)	0.0290(15)	0.0211(12)	0.0031(10)	0.0034(9)	0.0017(10)
	C(122)	0.0331(13)	0.0258(14)	0.0237(12)	0.0014(10)	-0.0005(9)	-0.0012(10)
	C(123)	0.0303(13)	0.0273(14)	0.0298(13)	-0.0024(10)	0.0030(10)	0.0004(11)
30	C(124)	0.0424(15)	0.056(2)	0.0253(14)	-0.0174(13)	0.0041(11)	0.0038(13)
	C(125)	0.058(2)	0.106(3)	0.0183(15)	-0.043(2)	-0.0035(13)	0.0069(16)
	C(126)	0.0371(15)	0.074(2)	0.0232(14)	-0.0218(14)	-0.0028(11)	0.0084(13)
	C(12A)	0.029(3)	0.049(4)	0.019(3)	-0.001(3)	0.002(2)	0.004(3)
	C(12B)	0.038(3)	0.047(4)	0.024(3)	-0.001(3)	0.006(3)	-0.001(3)
35	C(13A)	0.0548(18)	0.0415(18)	0.0357(16)	0.0079(13)	-0.0024(12)	-0.0088(13)
	C(13B)	0.0461(16)	0.048(2)	0.0341(15)	0.0134(13)	0.0017(12)	0.0084(13)

40 The form of the anisotropic temperature factor is: $\exp[-2\pi \{h^2 a'^2 U(1,1) + k^2 b'^2 U(2,2) + l^2 c'^2 U(3,3) + 2hka'b'U(1,2) + 2hla'c'U(1,3) + 2klb'c'U(2,3)\}]$, where a' , b' , and c' are reciprocal lattice constants.

Table 5
Bond Distances

	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
5	=====	=====	=====	=====	=====	=====
	S(1)	C(2)	1.702(3)	C(11)	C(12)	1.378(4)
	S(1)	C(5)	1.727(3)	C(12)	C(13)	1.375(3)
	O(6)	C(6)	1.235(3)	C(12)	C(121)	1.477(3)
10	O(122)	C(12A)	1.263(7)	C(121)	C(126)	1.390(4)
	O(122)	C(12B)	1.357(8)	C(121)	C(122)	1.394(3)
	N(8)	N(9)	1.339(3)	C(122)	C(123)	1.382(3)
	N(8)	C(13)	1.400(3)	C(123)	C(124)	1.384(4)
	N(8)	C(7)	1.406(3)	C(124)	C(125)	1.383(4)
15	N(9)	C(10)	1.312(4)	C(125)	C(126)	1.389(4)
	N(14)	C(15)	1.321(3)	C(125)	N(12B)	1.510(5)
	N(14)	C(13)	1.377(3)	C(125)	N(12A)	1.533(6)
	C(2)	C(3)	1.359(4)	N(12A)	C(12A)	1.355(7)
	C(3)	C(4)	1.396(4)	N(12A)	C(13A)	1.432(6)
20	C(4)	C(5)	1.372(4)	C(12A)	C(13B)	1.540(8)
	C(5)	C(6)	1.478(4)	N(12B)	C(12B)	1.343(8)
	C(6)	C(7)	1.460(3)	N(12B)	C(13B)	1.454(5)
	C(7)	C(15)	1.413(3)	C(12B)	C(13A)	1.494(8)
	C(10)	C(11)	1.421(4)			
25	-----					

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 6
Bond Angles

	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
5								
	C(2)	S(1)	C(5)	91.67(14)	C(126)	C(121)	C(122)	118.9(2)
	C(12A)	O(122)	C(12B)	42.2(4)	C(126)	C(121)	C(12)	122.0(2)
	N(9)	N(8)	C(13)	121.9(2)	C(122)	C(121)	C(12)	119.1(2)
10	N(9)	N(8)	C(7)	132.9(2)	C(123)	C(122)	C(121)	120.5(2)
	C(13)	N(8)	C(7)	105.3(2)	C(122)	C(123)	C(124)	121.0(2)
	C(10)	N(9)	N(8)	116.5(2)	C(125)	C(124)	C(123)	118.2(3)
	C(15)	N(14)	C(13)	103.91(19)	C(124)	C(125)	C(126)	121.7(3)
15	C(3)	C(2)	S(1)	112.0(2)	C(124)	C(125)	N(12B)	120.2(3)
	C(2)	C(3)	C(4)	112.8(3)	C(126)	C(125)	N(12B)	114.9(3)
	C(5)	C(4)	C(3)	113.0(3)	C(124)	C(125)	N(12A)	116.0(3)
	C(4)	C(5)	C(6)	133.6(2)	C(126)	C(125)	N(12A)	117.8(3)
	C(4)	C(5)	S(1)	110.5(2)	N(12B)	C(125)	N(12A)	40.2(2)
	C(6)	C(5)	S(1)	115.89(18)	C(125)	C(126)	C(121)	119.6(3)
20	O(6)	C(6)	C(7)	121.4(2)	C(12A)	N(12A)	C(13A)	120.9(5)
	O(6)	C(6)	C(5)	118.3(2)	C(12A)	N(12A)	C(125)	114.4(5)
	C(7)	C(6)	C(5)	120.3(2)	C(13A)	N(12A)	C(125)	124.5(4)
	N(8)	C(7)	C(15)	104.4(2)	O(122)	C(12A)	N(12A)	112.7(6)
	N(8)	C(7)	C(6)	124.9(2)	O(122)	C(12A)	C(13B)	130.8(5)
25	C(15)	C(7)	C(6)	130.7(2)	N(12A)	C(12A)	C(13B)	116.4(5)
	N(9)	C(10)	C(11)	124.4(2)	C(12B)	N(12B)	C(13B)	120.6(6)
	C(12)	C(11)	C(10)	119.7(3)	C(12B)	N(12B)	C(125)	110.2(5)
	C(13)	C(12)	C(11)	114.9(2)	C(13B)	N(12B)	C(125)	129.1(4)
	C(13)	C(12)	C(121)	121.7(2)	N(12B)	C(12B)	O(122)	110.2(6)
30	C(11)	C(12)	C(121)	123.4(2)	N(12B)	C(12B)	C(13A)	120.3(6)
	C(12)	C(13)	N(14)	125.07(19)	O(122)	C(12B)	C(13A)	129.5(5)
	C(12)	C(13)	N(8)	122.6(2)	N(12A)	C(13A)	C(12B)	33.8(3)
	N(14)	C(13)	N(8)	112.3(2)	N(12B)	C(13B)	C(12A)	37.9(3)
35	N(14)	C(15)	C(7)	114.1(2)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

40 In addition, Figure 3 shows the FT-Raman spectra of polymorph Form III as acquired on a Raman accessory module interfaced to a Magna 860[®] Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet). This module uses an excitation wavelength of 1064 nm and an indium gallium arsenide (InGaAs) detector. Approximately 0.5 W of Nd:YVO₄ laser power was used to irradiate the sample. The

45 samples were prepared for analysis by placing the material in a glass tube and positioning the tube in a gold-coated tube holder in the accessory. A total of 256 sample scans were collected from 3600 – 100 cm⁻¹ at a spectral resolution of 4 cm⁻¹, using Happ-Genzel apodization. Wavelength calibration was performed using sulfur and cyclohexane.

Polymorph Form III may be prepared by crystallization from a crystallization solvent containing Compound 1. As used herein, the term "crystallization solvent" means a solvent or combination of solvents from which Compound 1 is preferentially crystallized as polymorph Form III. Representative
5 crystallization solvents include polar solvents, nonpolar solvents, protic solvents and aprotic solvents, and more specifically include acetic acid, methylene chloride, acetone, methanol, ethanol, propanol, butanol, ethyl acetate, THF, DMF, diethyl ether, acetonitrile, toluene, water, and combinations thereof. In one embodiment, the crystallization solvent comprises acetic acid, to which water is gradually added.

10 Compound 1 may be introduced into the crystallization solvent in either a solid or liquid form. When added as a solid, Compound 1 may be in the form of a solid powder or any other solid form that aids its dissolution within the crystallization solvent. When added as a liquid, Compound 1 may first be dissolved in a co-solvent to yield a co-solvent solution, which is then combined with the crystallization solvent.
15 The concentration of Compound 1 within the co-solvent solution may range from 0.1% by weight to the saturation point. This concentration will, of course, vary depending upon the temperature at which the co-solvent solution is held, with warmer temperatures generally allowing for the preparation of more concentrated solutions of Compound 1. In general, the co-solvent should aid in the dissolution of Compound 1,
20 but not negatively interfere with the formation of polymorph Form III from the resulting crystallization solvent. Suitable co-solvents include the same solvents as identified above for the crystallization solvent. Further, the co-solvent and the crystallization solvent may be the same or different. For example, both the crystallization solvent and the co-solvent may be acetic acid, or they may be different solvents (or combinations
25 thereof).

In one embodiment, the co-solvent solution containing Compound 1 is added to the crystallization solvent or, alternatively, the crystallization solvent is added to the co-solvent solution. In still another embodiment, the co-solvent solution may be at or above ambient temperature (*e.g.*, heated), while the temperature of the
30 crystallization solvent may be below (*e.g.*, chilled), above (*e.g.*, heated) or at ambient temperature. Alternatively, the co-solvent solution can undergo a solvent exchange and

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form a solution or heterogeneous mixture of the crystallization solvent and Compound 1. For example, Compound 1 may be dissolved in a first solvent, followed by addition to a second solvent, and then followed by removal of all or part of the first solvent (e.g., by distillation).

5 Crystallization of polymorph Form III may be achieved by addition of carbon or other nucleating agent to the crystallization solvent containing Compound 1. As used herein, a "nucleating agent" means a substance that aids in the formation of "nuclei" around which a crystal grows. Such nuclei may occur spontaneously in a supersaturated crystalline solvent and then will grow into larger crystals. Formation of
10 the nuclei may also be induced by addition of a seed crystal or by the incidental or purposeful addition of some foreign solid matter such as dust or activated carbon. In a specific example (*see* Example 1 below), addition of a small amount of activated carbon to a heated solution of Compound 1 in acetic acid (60 mL) and water (70 mL), followed by subsequent cooling steps, yields polymorph Form III. The carbon may be added
15 either before or after the addition of the water to result in formation of polymorph Form III.

 Once obtained, crystals of polymorph Form III may be used as the nucleating agent or "seed" crystals for subsequent crystallizations of polymorph Form III from the crystallization solvent. In one embodiment, the crystallization solvent is
20 formed by dissolving Compound 1 in hot acetone or other suitable crystallization solvent. The crystallization solvent is then seeded with crystals of polymorph Form III, cooled and filtered, resulting in polymorph Form III. In another embodiment, a crystallization solvent is formed by slurring Compound 1 in acetone or other appropriate solvent. The crystallization solvent is then seeded with crystals of
25 polymorph Form III and filtered, resulting in polymorph Form III. Such seeding with crystals of polymorph Form III may take place at any time during the slurring process. Alternatively, seeding with crystals of polymorph Form III may take place prior to, or simultaneously with, addition of Compound 1 to the crystallization solvent.

 Crystals of polymorph Form III may also be used as the nucleating agent
30 or seed crystals in the conversion of a suspension or slurry of Compound 1 to produce polymorph Form III. Depending upon factors such as temperature, solvent and time, the

resulting Compound 1 may be predominantly polymorph Form III, or may be polymorphic mixtures of Compound 1.

For purposes of administration to a patient, polymorph Form III may be formulated as a pharmaceutical composition. Such pharmaceutical compositions
5 comprise polymorph Form III and one or more pharmaceutically acceptable carriers, wherein the polymorph is present in the composition in an amount that is effective to treat the condition of interest. Typically, the pharmaceutical compositions of the present invention include polymorph Form III in an amount ranging from 0.1 mg to 250
10 mg per dosage depending upon the route of administration, and more typically from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carriers are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and
15 other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain – in addition to polymorph Form III – diluents, dispersing and surface-active agents, binders, lubricants, and/or delayed releases agents. One skilled in this art may further formulate the polymorph in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's
20 Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990 (incorporated herein by reference in its entirety).

In another embodiment, the invention provides a method for treating conditions that benefit from administration of agents that possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic, anticonvulsant, and/or skeletal muscle relaxant
25 properties. Such conditions include insomnia specifically, as well as sleep disorders generally and other neurological and psychiatric complaints, anxiety states, vigilance disorders, such as for combating behavioral disorders attributable to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, epileptic vertigo attributable to cranial trauma, and for metabolic encephalopathies.

30 The methods of this invention include systemic administration of polymorph Form III, preferably in the form of a pharmaceutical composition. As used

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herein, systemic administration encompasses both oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets and capsules, as well as liquids, syrups, suspensions and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions that may contain buffers, antioxidants, bacteriostats and/or other additives commonly employed in such solutions.

The following examples are offered by way of illustration, not limitation.

10

EXAMPLES

EXAMPLE 1

REPRESENTATIVE SYNTHESIS OF POLYMORPH FORM III

Compound 1 (10 g) made according to the procedures of U.S. Patent No. 6,399,621 (incorporated herein by reference) was dissolved in 60 mL of acetic acid. The solution was then filtered and heated to 70-75°C. Water (70 mL) and carbon (Darco G-60, 5 mg) were added to the heated solution, and the resulting solution was then cooled 5°C every 30 minutes. At 55°C, crystallization began and the temperature was held steady for 30 minutes. The mixture was then cooled to 45-50°C and 40 mL of water was added. The mixture was further cooled to 25°C over a 1 hour period and the resulting solid was filtered and washed with 40 mL of water and dried to yield 9 g of polymorph Form III as a yellow solid (see Figures 1 and 2 for characterization of Polymorph Form III by DSC and X-ray powder diffraction).

EXAMPLE 2

REPRESENTATIVE SYNTHESIS OF POLYMORPH FORM III

Compound 1 (10 g) made according to the procedure of U.S. Patent No. 6,399,621 was dissolved in 60 mL of acetic acid. The solution was then filtered and heated to 70-75°C. Water (70 mL) was added to the heated solution. After cooling to 67°C, polymorph Form III seed crystals (as obtained by the procedure described in Example 1 above) were added and the mixture was cooled to 50°C over 2 hours. 40 mL

of water was added and the mixture was cooled to room temperature. The resulting solid was filtered and washed with 40 mL of water to yield 9 g of polymorph Form III as a yellow solid (DSC endotherm peak at 191.86°C).

EXAMPLE 3

5 REPRESENTATIVE SYNTHESIS OF POLYMORPH FORM III

Compound 1 (10 g) was prepared according to the procedure of U.S. Patent No. 6,399,621 and dissolved in 60 mL of acetic acid. The solution was then filtered and heated to 70-75°C. Water (70 mL) was added to the heated solution. After cooling to 52°C, polymorph Form III seed crystals (as obtained by the procedure
10 described in Example 1) were added and the mixture was stirred for 30 minutes. The mixture was then cooled to 47°C over 30 minutes followed by addition of 40 mL of water. Following cooling to room temperature, the resulting solid was filtered and washed with 40 mL of water to yield 9 g of polymorph Form III as a yellow solid (DSC endotherm peak at 191.68°C).

15 EXAMPLE 4

INTERCONVERSION OF COMPOUND 1

Interconversion experiments were carried out to evaluate the thermodynamic stability of Compound 1 at room temperature. Three slurries were prepared by making saturated isopropanol solutions of Compound 1, filtering the
20 solutions through 0.2µm filters, and then adding an amount (in the form of crystals) of a polymorphic form of Compound 1. To the first slurry, equal amounts of both polymorph Form II and polymorph Form III (*i.e.*, approximately 25 mg each) were added; to the second slurry, equal amounts of polymorph Form I and polymorph Form III (*i.e.*, approximately 25 mg each) were added; and to the third slurry, approximately
25 25 mg of polymorph Form III was added. The slurries were then agitated for 16 days. The resulting solids were collected by vacuum filtration, air-dried, and analyzed using XRPD. By the above technique, the first slurry seeded with polymorph Forms II and III yielded exclusively polymorph Form III. On the other hand, the second slurry seeded with polymorph Forms I and III yielded polymorph Form III as the predominant

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X

product, with only a minor amount of polymorph Form I. The third slurry seeded with polymorph Form III alone yielded exclusively polymorph Form III. These results indicate that Compound 1, when in a slurry form, will convert to polymorph Form III when seeded with crystals of the same, and under such conditions is the favored polymorph.

The above is a detailed description of particular embodiments of the invention. It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

1. Polymorph Form III of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide.
2. The polymorph Form III of claim 1 wherein the polymorph exhibits a predominant endotherm at about 191°C as measured by as measured by a TA 2920 Modulated Differential Scanning Calorimeter (DSC) at a scan rate of 10°C per minute.
3. The polymorph Form III of claim 1 wherein the polymorph exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ\theta$) at 18.9 and 28.1.
4. The polymorph Form III of claim 3 wherein the polymorph exhibits an additional characteristic peak expressed in degrees 2θ ($\pm 0.2^\circ\theta$) at 10.2.
5. The polymorph Form III of claim 4 wherein the polymorph exhibits additional characteristic peaks expressed in degrees 2θ ($\pm 0.2^\circ\theta$) at 13.3, 20.7, 22.2 and 30.8.
6. The polymorph Form III of claim 1 wherein the polymorph exhibits an X-ray powder diffraction pattern as shown in Figure 2.
7. The polymorph Form III of claim 1 wherein the polymorph exhibits a single crystal x-ray crystallographic analysis at 150°K with crystal parameters as the following:

Space Group	$P2_1/n$
$a, \text{\AA}$	9.5887(3)
$b, \text{\AA}$	10.3985(4)
$c, \text{\AA}$	17.5807(7)
α	90
β	96.8044(14)

γ	90
Z (molecules/unit cell)	4
Calculated Density (g/cm)	1.436

8. The polymorph Form III of claim 1 wherein the polymorph exhibits a Raman FT Infrared spectrum as shown in Figure 3.

9. The polymorph Form III of claim 1 wherein the polymorph contains less than 2% by weight total impurities, less than 1% by weight water, and less than 0.5% by weight organic solvent.

10. The polymorph Form III of claim 1 wherein the polymorph contains less than 1% by weight total impurities, less than about 0.75% by weight water, and less than 0.4% by weight residual organic solvent.

11. A composition comprising polymorph Form III of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide.

12. The composition of claim 11, further comprising N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide in a crystalline, solvate or amorphous form other than polymorph Form III.

13. The composition of claim 11 further comprising polymorph Form I.

14. The composition of claim 11 further comprising polymorph Form II.

15. A composition comprising polymorph Form III of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide in combination with a pharmaceutically acceptable carrier.

16. The composition of claim 15 wherein the composition is formulated for oral administration.

17. The composition of claim 16 wherein the composition is in the form of a pill, capsule or tablet.

18. The composition of claim 15 wherein polymorph Form III is present in the pill, capsule or table in a unit dosage form in an amount from 0.1 to 250 mg.

19. A composition comprising (a) polymorph Form III of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide ("Compound 1") and (b) a crystalline, solvate, amorphous or other form of Compound 1 other than polymorph Form III, wherein the total weight of Compound 1 in the composition is the sum of (a) plus (b).

20. The composition of claim 19 wherein the composition comprises less than 0.1% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

21. The composition of claim 19 wherein the composition comprises less than 0.5% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

22. The composition of claim 19 wherein the composition comprises less than 1% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

23. The composition of claim 19 wherein the composition comprises less than 2% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

24. The composition of claim 19 wherein the composition comprises less than 5% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

25. The composition of claim 19 wherein the composition comprises less than 10% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

26. The composition of claim 19 wherein the composition comprises less than 20% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

27. The composition of claim 19 wherein the composition comprises less than 30% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

28. The composition of claim 19 wherein the composition comprises less than 40% by weight of polymorph Form III based on the total weight of Compound 1 in the composition.

29. The composition of claim 19 wherein the composition comprises less than 50% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

30. The composition of claim 19 wherein the composition comprises at least 50% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

31. The composition of claim 19 wherein the composition comprises at least 60% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

32. The composition of claim 19 wherein the composition comprises at least 70% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

33. The composition of claim 19 wherein the composition comprises at least 80% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

34. The composition of claim 19 wherein the composition comprises at least 90% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

35. The composition of claim 19 wherein the composition comprises at least 95% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

36. The composition of claim 19 wherein the composition comprises at least 97% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

37. The composition of claim 19 wherein the composition comprises at least 98% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

38. The composition of claim 19 wherein the composition comprises at least 99% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

39. The composition of claim 19 wherein the composition comprises at least 99.5% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

40. The composition of claim 19 wherein the composition comprises at least 99.9% by weight of polymorph Form III based upon the total weight of Compound 1 in the composition.

41. The composition of claim 19 wherein the composition is in the form of a pill, capsule or tablet.

42. The composition of claim 19 wherein the composition is in the form of a slurry.

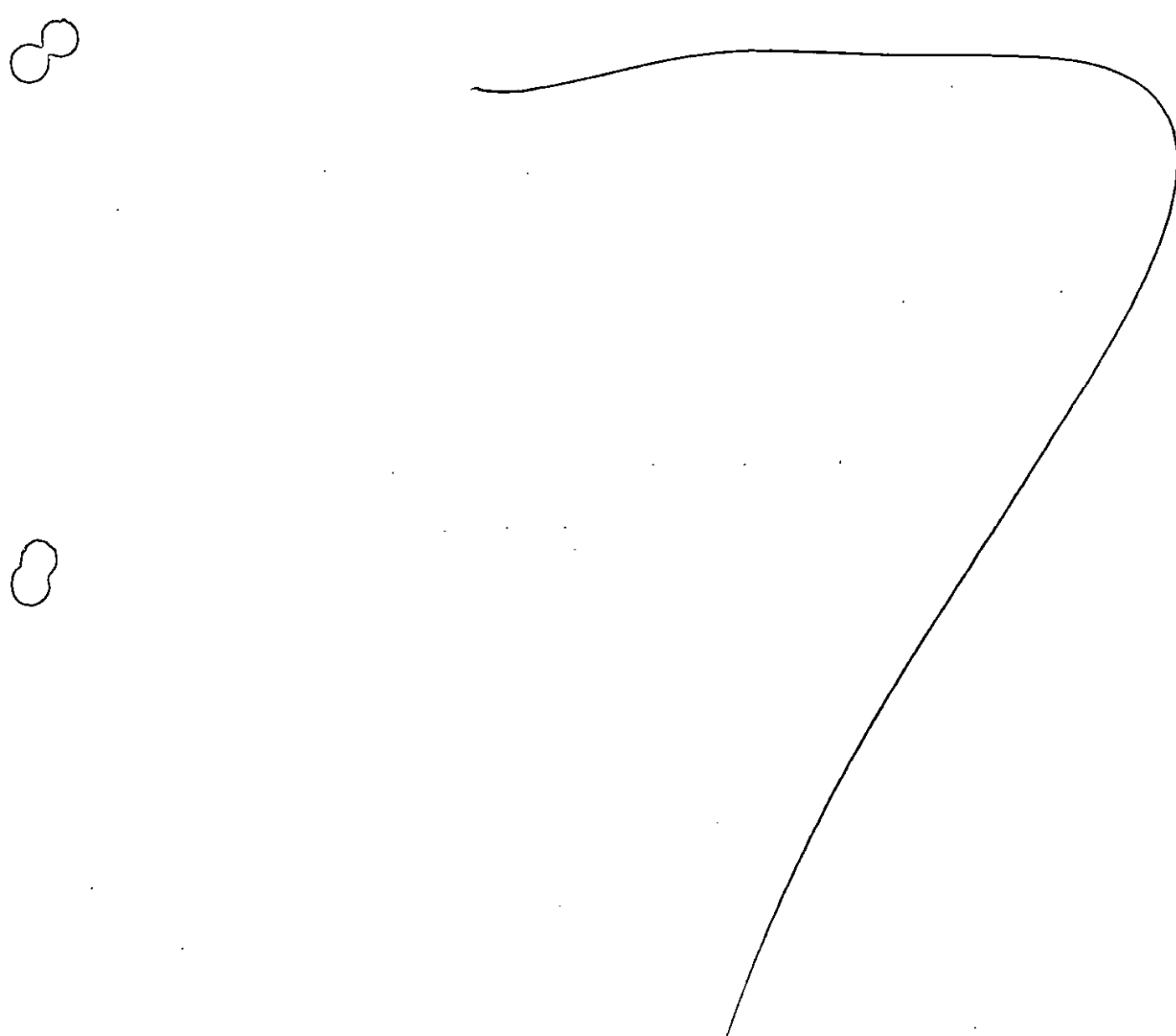
43. A method for treating insomnia in a patient in need thereof, comprising administering to the patient an effective amount of the composition of claim 15.

44. A method for inducing sleep in a patient in need thereof, comprising administering to the patient an effective amount of the composition of claim 15.

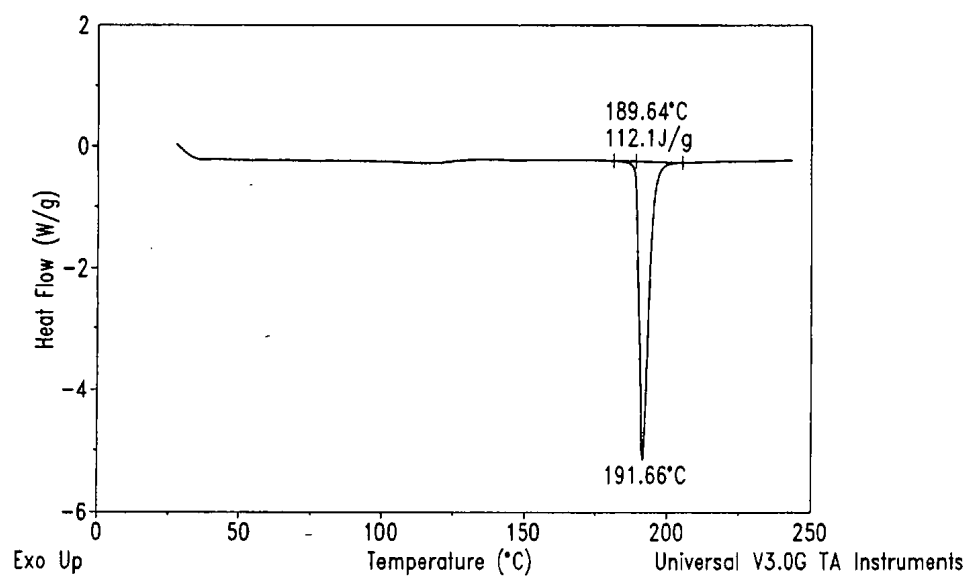
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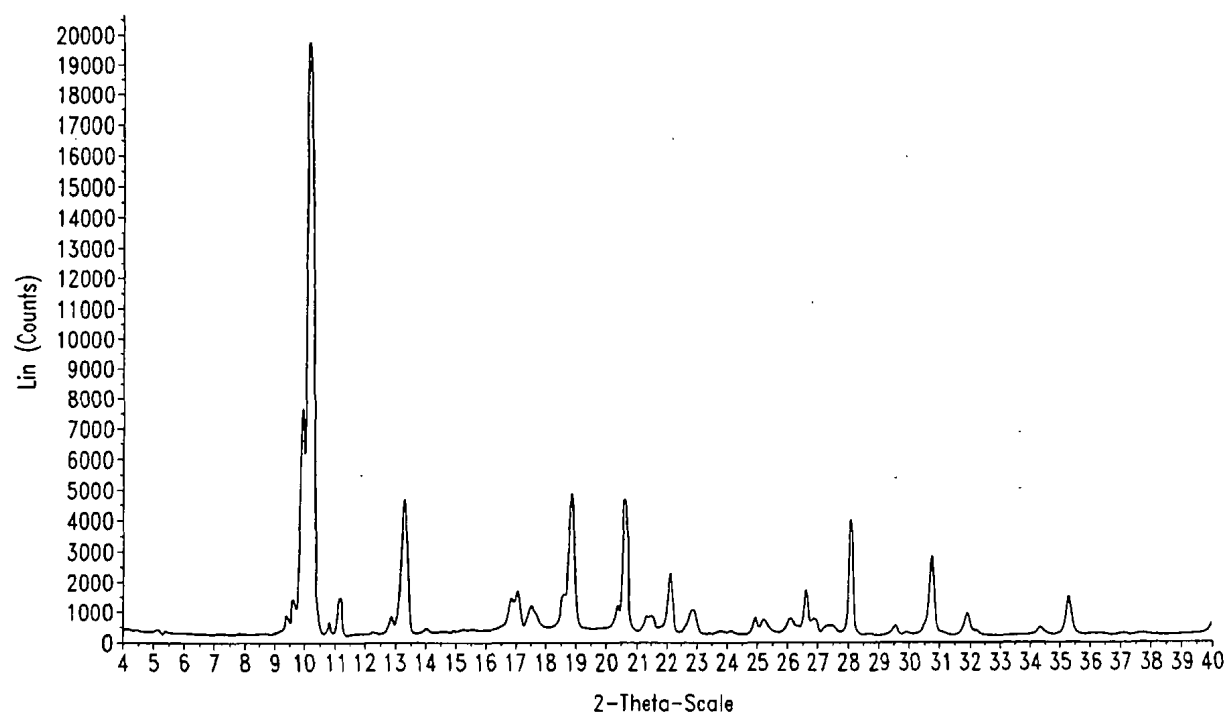
45. A method for inducing sedation or hypnosis in a patient in need thereof, comprising administering to the patient an effective amount of the composition of claim 15.

46. A method for inducing skeletal muscle relaxation in a patient in need thereof, comprising administering to the patient an effective amount of the composition of claim 15.



X

*FIG. 1*

*FIG. 2*

✓

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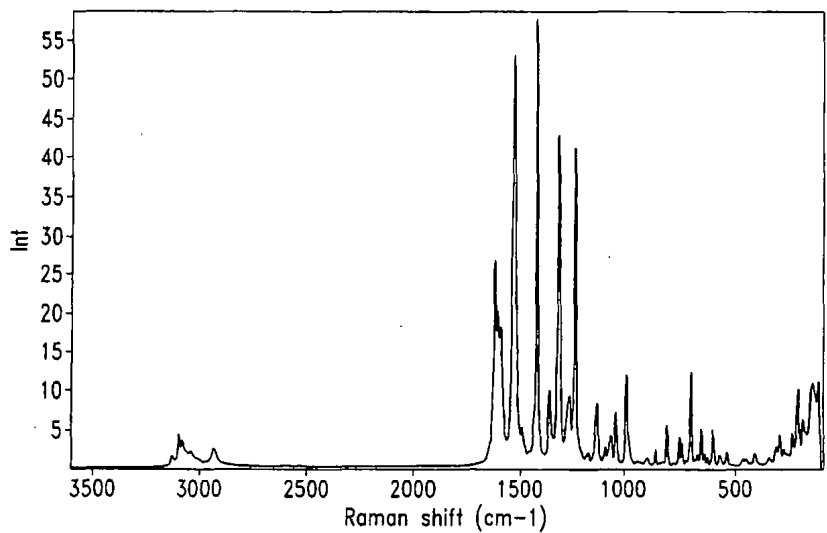


FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/26870

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/519 A61P25/00 //(C07D487/04,239:00,
231:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2002/107256 A1 (O'DONNELL PATRICK B ET AL) 8 August 2002 (2002-08-08) cited in the application claims -----	1,15, 43-46



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

21 November 2003

Date of mailing of the international search report

05/12/2003

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/26870

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

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

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

Although claims 43 - 46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/26870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002107256 A1	08-08-2002	US 6384221 B1	07-05-2002
		US 2003199524 A1	23-10-2003

23

POLIMORFO NOVEDOSO DEL N-METIL-N-(3-{3-[2-TIENILCARBONIL]-PIRAZOL-
[1,5- α]-PIRIMIDINA-7-YL} FENIL)ACETAMIDA
Y COMPUESTOS Y MÉTODOS RELACIONADOS

REFERENCIA CRUZADA A APLICACIÓN RELACIONADA

Esta aplicación reivindica la Solicitud Provisional EEUU (*U.S. Provisional Application*) N° 60/406,072 sometida el 26 de agosto de 2002, la cual se da por incorporada en su totalidad al presente documento mediante esta referencia.

CAMPO DE LA INVENCION

La presente invención se relaciona en general con un polimorfo novedoso del N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl} fenil)acetamida, el cual tiene actividad sobre un amplio rango de indicaciones y es particularmente útil en el tratamiento del insomnio y procesos relacionados, compuestos y métodos.

ANTECEDENTES DE LA INVENCION

El término "insomnio" se usa para describir todas las condiciones relacionadas con la percepción del paciente de un sueño inadecuado o no reparador (Dement, *International Pharmacopsychiatry* 17:3-38, 1982). De no tratarse, el insomnio puede producir disturbios en el metabolismo y en el funcionamiento del cuerpo en general, incluyendo una disminución de la productividad y cambios significativos en el humor, conducta y función psicomotora, y una mayor incidencia en la morbilidad y mortalidad.

Tradicionalmente el manejo del insomnio incluye tratamiento y/o mitigación de los factores etiológicos, mejoramiento de la higiene del sueño y la administración de agentes hipnóticos. Los primeros agentes hipnóticos, como los barbitúricos, aunque efectivos desencadenaban un espectro de efectos colaterales indeseables y complicaciones a largo plazo. Por ejemplo, los barbitúricos tienen el potencial de producir letargo, confusión,

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depresión y una variedad de otros efectos residuales muchas horas después de la dosis, así como un potencial para ser altamente adictivos.

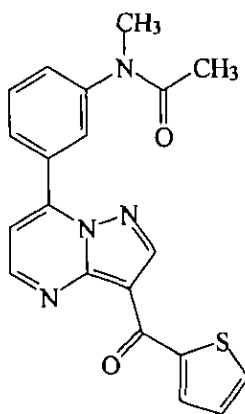
Durante los años ochenta el tratamiento farmacéutico del insomnio se desplazó de los barbitúricos y otros depresores CNS hacia la clase benzodiazepina de hipno-sedantes. Esta clase de agentes hipno-sedantes mostró efectividad sustancial para producir un efecto calmante que resulta en estados tipo sueño en humanos y animales (Gee et al., *Drogas en Sistemas Nerviosos Centrales -Drugs in Central Nervous Systems-*, Horwell (ed.), New York, Marcel Dekker, Inc., 1985, pags. 123-147) y un mayor margen de seguridad en comparación con hipnóticos anteriores, barbitúricos o hidrato de cloral (Cook and Sepinwall, *Mecanismo de Acción de las Benzodiazepinas -Mechanism of Action of Benzodiazepines-*, Costa and Greengard (eds.), New York, Raven Press, 1975, pags. 1-28). Sin embargo, al igual que los barbitúricos, las benzodiazepinas también tienen efectos colaterales que limitan su utilidad en ciertas poblaciones de pacientes. Estos problemas incluyen sinergia con otros depresores CNS (especialmente el alcohol), el desarrollo de tolerancia con la dosificación repetida, recaída del insomnio al discontinuar la dosificación, efectos de resaca al día siguiente y el impedimento de la acción psicomotora.

Más recientemente se ha desarrollado una nueva clase de agentes. Estos agentes son compuestos no-benzodiazepínicos que se enlazan selectivamente a un subtipo específico de receptor del receptor de la benzodiazepina. Se cree que esta selectividad en identificar el receptor es el mecanismo por el cual estos compuestos pueden ejercer un fuerte efecto hipnótico a la vez que muestran un perfil mejorado de seguridad en comparación con agentes no selectivos de la clase de las benzodiazepinas. El primero de estos agentes aprobado por la United States Food and Drug Administration (FDA) para su mercadeo en los Estados Unidos fue el Ambien (tartrato de zolpidem), el cual se basa en la estructura

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medular de la imidazopiridina (ver U.S. Patent Nos. 4,382,938 y 4,460,592). Además del Ambien otro compuesto conocido como Sonata (zaleplon), el cual está basado en la pirazolopirimidina, recibió aprobación de la FDA (ver U.S. Patent N° 4,626,538). Otros compuestos y/o métodos no-benzodiazepínicos, para preparar o usar los mismos, han sido reportados (ver, por ejemplo, 4,794,185, 4,808,594, 4,847,256, 5,714,607, 4,654,347; 5,891,891).

A pesar de los avances significativos hechos en este campo aún hay necesidad en el estado del arte de compuestos que sean efectivos como sedantes o agentes hipnóticos en general, particularmente en el contexto del tratamiento del insomnio. Un compuesto así es el N-metil-N-(3-{3-[2-tienilcarbonyl]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida (en adelante identificado como "Compuesto 1"). El Compuesto 1 aparece divulgado en la U.S. Patent No. 6,399,621 y tiene la siguiente estructura química:



Adicionalmente, las U.S. Patent N°s 6,384,221 y 6,544,999 están dirigidas a los polimorfos Forma I y Forma II del Compuesto 1, mientras que las U.S. Patent N°s

6,472,528 y 6,485,746 se refieren a la síntesis y a la liberación controlada, respectivamente, del Compuesto 1.

Aunque el Compuesto 1 ha probado ser particularmente prometedor en el tratamiento del insomnio, se requieren formas mejoradas de este compuesto, especialmente en relación a una solubilidad mejorada, biodisponibilidad oral, capacidad para ser fácilmente formulado, facilidad de síntesis y/o estabilidad física. La presente invención satisface una o más de estas necesidades y provee ventajas adicionales.

RESUMEN DE LA INVENCION

La presente invención se refiere en general a una forma polimórfica novedosa del Compuesto 1, denominada en este documento "polimorfo Forma III". El Polimorfo Forma III muestra un endotermo pico predominante alrededor de los 191°C (medidos con un Calorímetro de Muestreo Diferencial Modulado modelo TA 2920 [*TA 2920 Modulated Differential Scanning Calorimeter (DSC)*] a una tasa de muestreo de 10° por minuto). El polimorfo Forma III también presenta un patrón de Difracción de Polvo por Rayos-X [*X-ray Powder Diffraction pattern*] con picos característicos (expresados en grados 2θ (+/- $0,2^\circ\theta$) en una o más de las siguientes posiciones: 10.2, 13.3, 18.9, 20.7, 22.2, 28.1, y 30.8. Más específicamente, tales picos característicos están en 18.9 y 28.1, y más allá en 10.2, y más allá en 13.3, 20.7, 22.2 y 30.8.

El polimorfo Forma III es útil en un amplio rango de aplicaciones, incluyendo su utilidad como sedante y/o agente hipnótico general, y más específicamente, para el tratamiento del insomnio. Así, en otro documento, se divulgan métodos para el tratamiento de varias condiciones, incluyendo el insomnio, mediante la administración de una cantidad efectiva del polimorfo Forma III a un animal o un sujeto con tal necesidad (denominado en

este trabajo "paciente") y, típicamente, a un animal de sangre caliente (incluyendo a humanos).

En una presentación, el polimorfo Forma III es sustancialmente puro – es decir, con un contenido total de impurezas menor al 2% en peso, menos de un 1% en peso de agua, y menos del 0,5% en peso de solvente residual orgánico; o, en una presentación más específica, menos del 1% en peso de impurezas totales, menos de un 0,75% en peso de agua, y menos del 0,4% en peso de solvente residual orgánico.

En otra presentación, el Compuesto 1 está en forma de un compuesto o mezcla del polimorfo Forma III junto con una o más de otras formas cristalinas, solvatos, amorfas u otras formas del Compuesto 1. Por ejemplo, tal compuesto pudiera comprender el polimorfo Forma III junto con una o más formas polimórficas del Compuesto 1, tales como el polimorfo Forma I y/o el Forma II. Más específicamente, el compuesto puede comprender desde trazas hasta el 100% de polimorfo Forma III, o cualquier cantidad intermedia – por ejemplo, el compuesto puede comprender menos del 0,1%, 0,5%, 1%, 2%, 5%, 10%, 20%, 30%, 40% o 50% en peso del polimorfo Forma III con base en la cantidad total del Compuesto 1 en la composición. Alternativamente, el compuesto puede comprender al menos 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99%, 99,5%, o 99,9% en peso del polimorfo Forma III con base en la cantidad total del Compuesto 1 en el compuesto.

Antes de su administración, y en otra presentación, el polimorfo Forma III puede ser formulado como un compuesto farmacéutico que contiene una cantidad dosificada efectiva de polimorfo Forma III combinada con uno (o más) portadores farmacéuticos aceptables. Tales compuestos pueden asumir una variedad de formas, incluyendo pastillas, tabletas y cápsulas para administración oral.

En aún otra presentación, el compuesto farmacéutico comprende una cantidad dosificada efectiva de Compuesto 1, en el cual el Compuesto 1 comprende al menos cierto porcentaje del polimorfo Forma III (basado en la cantidad total del Compuesto 1 presente en el compuesto, es decir, siendo la cantidad total de Compuesto 1 un 100%). En otras palabras, al menos un cierto porcentaje del Compuesto 1 presente en el compuesto farmacéutico existe en la forma de polimorfo Forma III, con el resto del Compuesto 1 estando en forma diferente, incluyendo (pero no limitado a) polimorfo Forma I, polimorfo Forma II, o cualesquiera otras forma(s) cristalina, solvatos o amorfas.

En todavía otra presentación, esta invención provee procesos para fabricar el polimorfo Forma III. Por ejemplo, el polimorfo Forma III puede producirse mediante (a) la provisión de un solvente de cristalización calentado que comprenda el Compuesto 1, (b) agregando agua y un agente nucleante (como carbono o cristales de polimorfo Forma III) en cantidades suficientes para inducir la cristalización del polimorfo Forma III, y (c) recolectando polimorfo Forma III cristalizado. Más aún, el polimorfo Forma III hecho de acuerdo con uno o más de los procesos de esta invención también se divulga.

Estos y otros aspectos de esta invención resultarán evidentes al hacer referencia a la descripción detallada que se inserta a continuación junto con figuras. A tal efecto, en este documento se citan ciertas patentes y otros documentos para precisar más específicamente varios aspectos de esta invención. Cada uno de estos documentos se dan por incorporados en su totalidad mediante las referencias respectivas.

BREVE DESCRIPCIÓN DE LAS FIGURAS

La Figura 1 es un termograma por Calorimetría de Barrido Diferencial (*Differential Scanning Calorimetry* - DSC, siglas en inglés) del polimorfo Forma III.

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La Figura 2 es el Espectro de Difracción de Rayos-X por polvo (*X-ray Powder Diffraction Spectrum*) del polimorfo Forma III.

La figura 3 es el espectro infra-rojo FT Raman del polimorfo Forma III.

DESCRIPCIÓN DETALLADA DE LA INVENCION.

Tal como se mencionó anteriormente, la presente invención está dirigida, en general, a una forma polimórfica novedosa del Compuesto 1, denominada "polimorfo Forma III" en el presente documento, así como a compuestos que la contienen. También se divulgan métodos relacionados con el uso del polimorfo Forma III mediante su administración a pacientes que lo ameriten, y a procesos para hacer el polimorfo Forma III.

Existen sólidos tanto en formas amorfas como cristalinas. En el caso de formas cristalinas las moléculas se posicionan en retículas tridimensionales. Cuando un compuesto recristaliza a partir de una solución o una suspensión, puede que lo haga con disposiciones espaciales reticulares diferentes, una propiedad denominada "polimorfismo"; las diferentes formas cristalinas se conocen como "polimorfos". Las diferentes formas polimórficas de una sustancia dada pueden diferir entre sí con respecto a una o más propiedades físicas, tales como solubilidad o disociación, densidad verdadera, forma del cristal, comportamiento de compactación, propiedades de flujo y/o estabilidad del estado sólido. En el caso de una sustancia química que existe en dos (o más) formas polimórficas, las formas inestables generalmente se convierten en las formas más termodinámicamente estables, a una temperatura dada y después de un tiempo suficiente. Cuando esta transformación no es rápida, la forma termodinámicamente inestable se denomina forma "metaestable". En general, la forma estable presenta el punto de fusión más alto, la menor solubilidad y la máxima estabilidad química. Sin embargo, la forma metaestable puede tener suficiente estabilidad química y física bajo condiciones normales de almacenamiento

como para permitir su uso comercial. En este caso, la forma metaestable, aunque menos estable, puede presentar propiedades deseables superiores a las de la forma estable, tales como solubilidad mejorada o mejor biodisponibilidad oral.

En el caso del Compuesto 1, dos formas polimórficas (Forma I y Forma II) han sido previamente reportadas (ver U.S. Patents Nos. 6,384,221 y 6,544,999). El Compuesto 1 está actualmente siendo sometido a pruebas clínicas en el tratamiento del insomnio. Anticipando una potencial producción a gran escala ha habido un significativo esfuerzo dirigido a la producción a escala comercial del Compuesto 1. Durante una de tales corridas de producción se descubrió una impureza en el producto final. En el esfuerzo por eliminar la impureza se agregó carbono seguido de una recrystalización. Como resultado de este trabajo subsiguiente se descubrió con sorpresa la obtención de un nuevo polimorfo (el polimorfo Forma III). Aunque sin la intención de verse limitados por la teoría, se cree que el carbono agregado sirvió como punto de nucleación para la formación del Compuesto 1.

El novedoso y sorprendente polimorfo de esta invención, el polimorfo Forma III, puede ser caracterizado, por ejemplo, por su punto de fusión y/o por espectrometría de Rayos-X de difracción por polvo. Como se muestra en la Figura 1, el polimorfo Forma III presenta un endotermo pico predominante cerca de los 190°C, medidos con un Calorímetro de Muestreo Diferencial Modulado (DSC, siglas en inglés), modelo TA 2920 de la TA Instruments, New Castle, Delaware), a una tasa de muestreo de 10°C por minuto con un patrón de Indio. Tal como se usa en el presente documento "cerca de los 190°C" significa un rango entre 190° y 192,5°C. Al respecto debe entenderse que el endotermo medido con un calorímetro de muestreo diferencial en particular depende de una serie de factores que incluyen la rata de calentamiento (es decir, la rata de muestreo), el patrón de calibración utilizado, el instrumento de calibración, la humedad relativa, y la pureza química de la

muestra que se ensaya. Por ello, el endotermo medido con el instrumento DSC antes mencionado puede variar tanto como $\pm 1^{\circ}\text{C}$, o inclusive $\pm 1\frac{1}{2}^{\circ}\text{C}$. En consecuencia, el término "cerca de los 190°C " busca abarcar tales variaciones instrumentales. En la Figura 2 se presenta el espectro de difracción de Rayos-X por polvo y más adelante se muestra en forma tabular en la Tabla 1. La difracción de Rayos-X por polvo se midió con un Difractómetro Automático de Polvo Siemens D500 equipado con un monocromador de grafito y una fuente Cu de Rayos-X ($\lambda=1,54$ Angstrom) operada a 50kV, 40mA. Se aplicó calibración dos-theta usando un patrón de mica NBS. La muestra fue analizada utilizando los siguientes parámetros instrumentales: rango de medición = $4-40^{\circ} 2\theta$; ancho del paso = $0,050^{\circ}$; y tiempo de medición por paso = 1,2 segundos.

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TABLA 1
Líneas espectrales de difracción de Rayos-X por polvo

<u>Valor d</u>	<u>2-θ</u>	<u>Intensidad</u>	<u>Intensidad %</u>
9.15587	9.652	1388	7.0
8.91589	9.912	7718	39.1
8.65670	10.210	19744	100.0
8.16181	10.831	572	2.9
7.88947	11.206	1398	7.1
6.85166	12.910	765	3.9
6.64840	13.306	4690	23.8
6.29329	14.081	396	2.0
5.24469	16.891	1398	7.1
5.19705	17.047	1731	8.8
5.05094	17.544	1170	5.9
4.76647	18.600	1567	7.9
4.69634	18.880	4865	24.6
4.34978	20.400	1131	5.7
4.29694	20.654	4611	23.4
4.12546	21.522	758	3.8
4.00186	22.195	2281	11.6
3.87889	22.908	1046	5.3
3.72796	23.849	321	1.6
3.56593	24.950	752	3.8
3.51637	25.307	716	3.6
3.40208	26.172	781	4.0
3.34446	26.631	1738	8.8
3.30597	26.947	764	3.9
3.23885	27.516	544	2.8
3.17029	28.124	4022	20.4
3.01819	29.572	480	2.4
2.97878	29.973	264	1.3

2.89811	30.827	2802	14.2
2.79651	31.977	890	4.5
2.77443	32.238	354	1.8
2.60380	34.415	407	2.1
2.53630	35.360	1434	7.3
2.41973	37.124	262	1.3
2.38437	37.695	253	1.3

La estructura cristalina del polimorfo Forma III fue determinada mediante análisis de difracción de Rayos-X de un solo cristal. Una placa sin color del polimorfo Forma III, de dimensiones 0,30 x 0,20 x 0,13 mm, se montó en una fibra de vidrio con orientación aleatoria. El exámen preliminar y la colección de data se realizaron con radiación Mo K_α ($\lambda=0,71073$ Å) en un difractómetro Nonius KappaCCD. La data correspondiente a la cristalografía de Rayos-X de un solo cristal del polimorfo Forma III se muestran a continuación en las tablas 2-6.

Tabla 2
Parámetros del cristal

Grupo Espacial	$P2_1/n$
a , Å	9.5887(3)
b , Å	10.3985(4)
c , Å	17.5807(7)
α	90

34

β	96,8044(14)
γ	90
Z (moléculas/celda unitaria)	4
Densidad calculada (g/cm)	1.436
Temperatura (K)	150

Tabla 3
Parámetros posicionales y sus desviaciones estándar estimadas

Átomo	x	y	z	U (Å²)
S(1)	0.46180(7)	-0.27982(8)	0.14578(4)	0.0384(2)
O(6)	0.62938(19)	-0.0547(2)	0.18402(10)	0.0382(6)
O(122)	0.8323(3)	0.2180(3)	-0.36178(12)	0.0643(8)
N(8)	0.7964(2)	0.1011(2)	0.09047(13)	0.0405(7)
N(9)	0.8076(2)	0.1723(2)	0.15438(12)	0.0317(6)
N(14)	0.8428(2)	0.0463(2)	-0.03115(11)	0.0286(6)
N(12A)	0.9717(5)	0.2278(5)	-0.2546(3)	0.0282(12)
N(12B)	0.9122(5)	0.3116(5)	-0.2521(3)	0.0319(14)
C(2)	0.3830(3)	-0.3736(3)	0.07383(18)	0.0420(9)
C(3)	0.4087(3)	-0.3309(3)	0.00378(17)	0.0391(8)
C(4)	0.4960(3)	-0.2230(3)	0.00787(16)	0.0331(7)
C(5)	0.5358(2)	-0.1829(3)	0.08160(14)	0.0294(7)
C(6)	0.6305(2)	-0.0805(3)	0.11554(13)	0.0280(7)
C(7)	0.7219(2)	-0.0121(2)	0.06857(13)	0.0264(7)
C(10)	0.8880(3)	0.2745(3)	0.15515(15)	0.0333(7)
C(11)	0.9616(3)	0.3131(3)	0.09337(14)	0.0311(7)
C(12)	0.9484(2)	0.2422(3)	0.02666(14)	0.0269(6)
C(13)	0.8667(2)	0.1337(2)	0.02781(11)	0.0154(5)
C(15)	0.7574(3)	-0.0389(3)	-0.00555(14)	0.0289(7)
C(121)	1.0127(3)	0.2801(2)	-0.04226(14)	0.0272(7)
C(122)	1.1408(2)	0.3451(2)	-0.03341(14)	0.0278(7)
C(123)	1.2019(3)	0.3852(3)	-0.09671(14)	0.0292(7)
C(124)	1.1380(3)	0.3615(3)	-0.17015(16)	0.0412(8)
C(125)	1.0100(4)	0.2988(4)	-0.17857(16)	0.0614(11)
C(126)	0.9462(3)	0.2586(3)	-0.11575(16)	0.0453(8)
C(12A)	0.8662(6)	0.2827(7)	-0.3016(3)	0.0324(17)
C(12B)	0.9236(7)	0.2085(7)	-0.2969(4)	0.0361(17)
C(13A)	1.0305(3)	0.1070(3)	-0.27368(17)	0.0446(9)
C(13B)	0.8135(3)	0.4141(3)	-0.27623(17)	0.0430(9)
H(2)	0.328	-0.447	0.082	0.050
H(3)	0.371	-0.370	-0.043	0.047
H(4)	0.525	-0.182	-0.036	0.040
H(10)	0.898	0.326	0.200	0.040
H(11)	1.020	0.387	0.098	0.037
H(15)	0.723	-0.112	-0.034	0.035
H(122)	1.186	0.362	0.016	0.033
H(123)	1.289	0.430	-0.090	0.035
H(124)	1.181	0.388	-0.214	0.049
H(126)	0.857	0.217	-0.123	0.055

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Los hidrógenos se incluyeron en el cálculo de los factores estructurales pero no se refinaron.

Tabla 4
Coefficientes del Factor de Temperatura Anisotrópica

Nombre	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
S(1)	0.0396(4)	0.0424(5)	0.0333(4)	-0.0081(3)	0.0048(3)	0.0054(3)
O(6)	0.0505(11)	0.0416(12)	0.0240(10)	-0.0064(9)	0.0105(8)	-0.0006(8)
O(122)	0.0705(15)	0.096(2)	0.0248(11)	-0.0246(14)	-0.0014(10)	-0.0111(12)
N(8)	0.0482(14)	0.0424(15)	0.0313(13)	0.0033(11)	0.0067(10)	0.0017(11)
N(9)	0.0430(12)	0.0308(13)	0.0220(11)	0.0035(10)	0.0067(9)	-0.0032(9)
N(14)	0.0346(11)	0.0299(12)	0.0215(10)	-0.0007(9)	0.0039(8)	-0.0037(9)
N(12A)	0.035(2)	0.035(3)	0.013(2)	0.000(2)	-0.0042(19)	0.0008(19)
N(12B)	0.035(2)	0.036(3)	0.024(3)	0.005(2)	0.0010(19)	0.006(2)
C(2)	0.0354(14)	0.0386(18)	0.0512(19)	-0.0088(12)	0.0014(12)	0.0004(14)
C(3)	0.0359(15)	0.0408(18)	0.0386(16)	-0.0010(12)	-0.0037(11)	-0.0033(13)
C(4)	0.0315(13)	0.0382(17)	0.0288(14)	0.0034(11)	-0.0002(10)	-0.0007(12)
C(5)	0.0295(13)	0.0312(15)	0.0275(13)	0.0042(10)	0.0036(10)	0.0036(11)
C(6)	0.0314(13)	0.0292(14)	0.0233(13)	0.0033(10)	0.0030(9)	0.0025(10)
C(7)	0.0336(13)	0.0252(14)	0.0208(12)	0.0038(10)	0.0043(9)	0.0018(10)
C(10)	0.0452(15)	0.0324(16)	0.0228(13)	-0.0004(12)	0.0061(11)	-0.0033(11)
C(11)	0.0396(14)	0.0300(14)	0.0236(12)	-0.0006(11)	0.0038(10)	-0.0019(11)
C(12)	0.0291(12)	0.0308(14)	0.0208(12)	0.0034(10)	0.0029(9)	0.0023(10)
C(13)	0.0207(10)	0.0169(11)	0.0089(9)	0.0014(8)	0.0030(7)	-0.0004(8)
C(15)	0.0358(13)	0.0282(14)	0.0227(12)	0.0010(10)	0.0031(9)	-0.0011(10)
C(121)	0.0317(13)	0.0290(15)	0.0211(12)	0.0031(10)	0.0034(9)	0.0017(10)
C(122)	0.0331(13)	0.0258(14)	0.0237(12)	0.0014(10)	-0.0005(9)	-0.0012(10)
C(123)	0.0303(13)	0.0273(14)	0.0298(13)	-0.0024(10)	0.0030(10)	0.0004(11)
C(124)	0.0424(15)	0.056(2)	0.0253(14)	-0.0174(13)	0.0041(11)	0.0038(13)
C(125)	0.058(2)	0.106(3)	0.0183(15)	-0.043(2)	-0.0035(13)	0.0069(16)
C(126)	0.0371(15)	0.074(2)	0.0232(14)	-0.0218(14)	-0.0028(11)	0.0084(13)
C(12A)	0.029(3)	0.049(4)	0.019(3)	-0.001(3)	0.002(2)	0.004(3)
C(12B)	0.038(3)	0.047(4)	0.024(3)	-0.001(3)	0.006(3)	-0.001(3)
C(13A)	0.0548(18)	0.0415(18)	0.0357(16)	0.0079(13)	-0.0024(12)	-0.0088(13)
C(13B)	0.0461(16)	0.048(2)	0.0341(15)	0.0134(13)	0.0017(12)	0.0084(13)

La forma del factor de temperatura anisotrópica es: $\exp[-2\pi \{h^2 a^{*2} U(1,1) + k^2 b^{*2} U(2,2) + l^2 c^{*2} U(3,3) + 2hka^*b^*U(1,2) + 2hla^*c^*U(1,3) + 2klb^*c^*U(2,3)\}]$, donde a^* , b^* y c^* son constantes reticulares recíprocas.

Table 5
Distancias de los Enlaces

Átomo 1	Átomo 2	Distancia	Átomo 1	Átomo 2	Distancia
=====	=====	=====	=====	=====	=====
S(1)	C(2)	1.702(3)	C(11)	C(12)	1.378(4)
S(1)	C(5)	1.727(3)	C(12)	C(13)	1.375(3)
O(6)	C(6)	1.235(3)	C(12)	C(121)	1.477(3)
O(122)	C(12A)	1.263(7)	C(121)	C(126)	1.390(4)
O(122)	C(12B)	1.357(8)	C(121)	C(122)	1.394(3)
N(8)	N(9)	1.339(3)	C(122)	C(123)	1.382(3)
N(8)	C(13)	1.400(3)	C(123)	C(124)	1.384(4)
N(8)	C(7)	1.406(3)	C(124)	C(125)	1.383(4)
N(9)	C(10)	1.312(4)	C(125)	C(126)	1.389(4)
N(14)	C(15)	1.321(3)	C(125)	N(12B)	1.510(5)
N(14)	C(13)	1.377(3)	C(125)	N(12A)	1.533(6)
C(2)	C(3)	1.359(4)	N(12A)	C(12A)	1.355(7)
C(3)	C(4)	1.396(4)	N(12A)	C(13A)	1.432(6)
C(4)	C(5)	1.372(4)	C(12A)	C(13B)	1.540(8)
C(5)	C(6)	1.478(4)	N(12B)	C(12B)	1.343(8)
C(6)	C(7)	1.460(3)	N(12B)	C(13B)	1.454(5)
C(7)	C(15)	1.413(3)	C(12B)	C(13A)	1.494(8)
C(10)	C(11)	1.421(4)			

Los números entre paréntesis son las desviaciones estándar estimadas de los dígitos menos significativos.

Tabla 6
Ángulos de los Enlaces

Átomo 1	Átomo 2	Átomo 3	Ángulo	Átomo 1	Átomo 2	Átomo 3	Ángulo
C(2)	S(1)	C(5)	91.67(14)	C(126)	C(121)	C(122)	118.9(2)
C(12A)	O(122)	C(12B)	42.2(4)	C(126)	C(121)	C(12)	122.0(2)
N(9)	N(8)	C(13)	121.9(2)	C(122)	C(121)	C(12)	119.1(2)
N(9)	N(8)	C(7)	132.9(2)	C(123)	C(122)	C(121)	120.5(2)
C(13)	N(8)	C(7)	105.3(2)	C(122)	C(123)	C(124)	121.0(2)
C(10)	N(9)	N(8)	116.5(2)	C(125)	C(124)	C(123)	118.2(3)
C(15)	N(14)	C(13)	103.91(19)	C(124)	C(125)	C(126)	121.7(3)
C(3)	C(2)	S(1)	112.0(2)	C(124)	C(125)	N(12B)	120.2(3)
C(2)	C(3)	C(4)	112.8(3)	C(126)	C(125)	N(12B)	114.9(3)
C(5)	C(4)	C(3)	113.0(3)	C(124)	C(125)	N(12A)	116.0(3)
C(4)	C(5)	C(6)	133.6(2)	C(126)	C(125)	N(12A)	117.8(3)
C(4)	C(5)	S(1)	110.5(2)	N(12B)	C(125)	N(12A)	40.2(2)
C(6)	C(5)	S(1)	115.89(18)	C(125)	C(126)	C(121)	119.6(3)
O(6)	C(6)	C(7)	121.4(2)	C(12A)	N(12A)	C(13A)	120.9(5)
O(6)	C(6)	C(5)	118.3(2)	C(12A)	N(12A)	C(125)	114.4(5)
C(7)	C(6)	C(5)	120.3(2)	C(13A)	N(12A)	C(125)	124.5(4)
N(8)	C(7)	C(15)	104.4(2)	O(122)	C(12A)	N(12A)	112.7(6)
N(8)	C(7)	C(6)	124.9(2)	O(122)	C(12A)	C(13B)	130.8(5)
C(15)	C(7)	C(6)	130.7(2)	N(12A)	C(12A)	C(13B)	116.4(5)
N(9)	C(10)	C(11)	124.4(2)	C(12B)	N(12B)	C(13B)	120.6(6)
C(12)	C(11)	C(10)	119.7(3)	C(12B)	N(12B)	C(125)	110.2(5)
C(13)	C(12)	C(11)	114.9(2)	C(13B)	N(12B)	C(125)	129.1(4)
C(13)	C(12)	C(121)	121.7(2)	N(12B)	C(12B)	O(122)	110.2(6)

C(11)	C(12)	C(121)	123.4(2)	N(12B)	C(12B)	C(13A)	120.3(6)
C(12)	C(13)	N(14)	125.07(19)	O(122)	C(12B)	C(13A)	129.5(5)
C(12)	C(13)	N(8)	122.6(2)	N(12A)	C(13A)	C(12B)	33.8(3)
N(14)	C(13)	N(8)	112.3(2)	N(12B)	C(13B)	C(12A)	37.9(3)
N(14)	C(15)	C(7)	114.1(2)				

Los números entre paréntesis son las desviaciones estándar estimadas de los dígitos menos significativos.

Adicionalmente, la Figura 3 muestra el espectro FT-Raman del polimorfo Forma III tal como fue obtenido con un módulo accesorio Raman conectado a un espectrómetro Magna 860® (Thermo Nicolet) de infrarrojo por transformada de Fourier (FT-IR). Este módulo utiliza una longitud de onda de excitación de 1064 nm y un detector de indio galio arsénico (InGaAs). Se utilizó aproximadamente 0,5 W de Nd:YVO₄ de potencia de láser para irradiar la muestra. Las muestras fueron preparadas para el análisis colocando el material en un tubo de vidrio y éste en un porta-tubos dorado en el accesorio. Se obtuvieron un total de 256 escaneos de muestra de 3600 – 100 cm⁻¹ con una resolución espectral de 4 cm⁻¹, aplicando apodización Happ-Genzel. La calibración de la longitud de onda se realizó usando azufre y ciclohexano.

El polimorfo Forma III puede ser preparado para cristalización a partir de un solvente de cristalización que contenga Compuesto 1. En el presente trabajo, el término “solvente de cristalización” significa un solvente o combinación de solventes de los cuales el Compuesto 1 se cristaliza preferentemente como polimorfo Forma III. Solventes de cristalización representativos incluyen los solventes polares, solventes no polares, solventes próticos y no próticos, y más específicamente incluyen el ácido acético, el cloruro de metileno, acetona, metanol, etanol, propanol, butanol, etil acetato, THF, DMF, dietil éter, acetonitrilo, tolueno, agua y cualquier combinación de éstos. En una presentación el solvente de cristalización comprende ácido acético al cual se le agrega agua gradualmente.

El Compuesto 1 puede ser introducido en el solvente de cristalización en forma sólida o líquida. Cuando se agrega en forma sólida, el Compuesto 1 puede estar en forma de un polvo sólido u cualquier otra forma sólida que ayude a su disolución dentro del solvente de cristalización. Cuando se agrega en forma líquida, el Compuesto 1 puede ser disuelto primero en un cosolvente para producir una solución cosolvente la cual es entonces

combinada con el solvente de cristalización. La concentración de Compuesto 1 en la solución cosolvente puede variar entre 0,1% en peso hasta el punto de saturación. Esta concentración, evidentemente, variará dependiendo de la temperatura a la cual se mantenga la solución cosolvente, las temperaturas más altas generalmente permitiendo la preparación de soluciones más concentradas de Compuesto 1. En general, el cosolvente debe ayudar a la disolución del Compuesto 1 pero no interferir negativamente en la formación del polimorfo Forma III del solvente de cristalización resultante. Cosolventes adecuados incluyen a los mismos solventes identificados antes para el solvente de cristalización. Más aún, el cosolvente y el solvente de cristalización pueden ser el mismo o diferentes. Por ejemplo, tanto el solvente de cristalización como el cosolvente pueden ser ácido acético, o pueden ser diferentes solventes (o combinaciones de los mismos).

En una presentación, la solución cosolvente que contiene Compuesto 1 se agrega al solvente de cristalización o, alternativamente, éste último se agrega a la solución cosolvente. En otra presentación, la solución cosolvente puede estar a o por encima de la temperatura ambiente (es decir, calentada), mientras que la temperatura del solvente de cristalización puede estar por debajo (es decir, enfriada), por encima (es decir, calentada) o a temperatura ambiente. Alternativamente, la solución cosolvente puede sufrir un cambio de solvente y formar una solución o mezcla heterogénea del solvente de cristalización y el Compuesto 1. Por ejemplo, el Compuesto 1 puede ser disuelto en un primer solvente, seguido de la adición a un segundo solvente y luego la remoción de todo o parte del primer solvente (es decir, por destilación).

La cristalización del polimorfo Forma III se puede lograr agregando carbono u otro agente nucleante al solvente de cristalización que contiene el Compuesto 1. En el presente trabajo se utiliza "agente nucleante" para identificar una sustancia que ayuda a la formación

de "núcleos" alrededor de los cuales crecen cristales. Tales núcleos pueden ocurrir espontáneamente en un solvente cristalino sobresaturado para luego crecer a mayores tamaños. La formación de núcleos también puede ser inducida agregando un cristal semilla o por la incidental o intencional adición de alguna materia extraña tal como polvo o carbón activado. En un ejemplo específico (ver Ejemplo 1 más adelante), la adición de una pequeña cantidad de carbón activado a la solución calentada del Compuesto 1 con ácido acético (60mL) y agua (70 mL), seguida de subsecuentes pasos de enfriamiento, produce el polimorfo Forma III. El carbono se puede agregar antes o después de la adición del agua para lograr la formación del polimorfo Forma III.

Una vez obtenidos, los cristales de polimorfo Forma III pueden usarse como agente nucleante o "semillas" de cristales para cristalizaciones subsecuentes de polimorfo Forma III a partir del solvente de cristalización. En una presentación, el solvente de cristalización se forma disolviendo Compuesto 1 en acetona caliente u otro solvente de cristalización adecuado. El solvente de cristalización es entonces sembrado con cristales de polimorfo Forma III, enfriado y filtrado, dando como resultado polimorfo Forma III. En otra presentación, el solvente de cristalización se forma preparando una suspensión (*slurrying*) del Compuesto 1 en acetona u otro solvente apropiado. Seguidamente el solvente de cristalización es sembrado con cristales de polimorfo Forma III y filtrado, dando como resultado polimorfo Forma III. La siembra con cristales de polimorfo Forma III puede hacerse en cualquier momento del proceso de preparación de la suspensión (*slurrying*). Alternativamente, la siembra de cristales de polimorfo Forma III puede hacerse antes de, o simultáneamente con, la adición de Compuesto 1 al solvente de cristalización.

Los cristales de polimorfo Forma III también pueden usarse como agente nucleante o semillas de cristal en la conversión de una solución concentrada o una suspensión (*slurry*)

de Compuesto 1 para producir polimorfo Forma III. Dependiendo de factores como la temperatura, el solvente y el tiempo, el Compuesto 1 resultante puede ser predominantemente polimorfo Forma III, o puede ser mezclas polimórficas de Compuesto 1.

Para su administración a un paciente, el polimorfo Forma III puede ser formulado como un compuesto farmacéutico. Tales compuestos farmacéuticos comprenden polimorfo Forma III y uno o más portadores farmacéuticos aceptables, donde el polimorfo está presente en el compuesto en una cantidad que es efectiva para tratar la condición de interés. Típicamente, los compuestos farmacéuticos de la presente invención incluyen polimorfo Forma III en una cantidad que oscila entre 0,1 mg y 250 mg por dosis, dependiendo de la ruta de administración, y más típicamente de 1 a 60 mg. Concentraciones y dosis adecuadas pueden ser fácilmente determinadas por alguien experto en la materia.

Los portadores farmacéuticos aceptables son conocidos por los expertos en la materia. Para compuestos formulados como soluciones líquidas, los portadores aceptables incluyen solución salina y estéril, y puede opcionalmente incluir antioxidantes, neutralizantes, bacteriostáticos, así como otros aditivos comunes. Los compuestos también pueden ser formulados como pastillas, cápsulas, gránulos, o tabletas que contengan –además de polimorfo Forma III– diluentes, dispersantes, surfactantes, aglutinantes, lubricantes, y/o agentes de liberación controlada. Un experto en este arte puede formular el polimorfo de una manera adecuada y de acuerdo con prácticas aceptadas, tales como las divulgadas en Remington's Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990 (Incorporadas en su totalidad a este trabajo mediante esta referencia).

En otra presentación, la invención provee un método para tratar condiciones que se benefician de la administración de agentes que posean propiedades ansiolíticas, anti-

anóxicas, soporíferas, hipnóticas, anticonvulsivante, y/o relajantes de músculos del esqueleto. Tales condiciones incluyen, expresamente, el insomnio, así como desórdenes del sueño en general y otras molestias neurológicas y psiquiátricas, estados de ansiedad, desórdenes de la vigilia, tales como para combatir desórdenes de conducta atribuibles a daños cerebrovasculares y a la esclerosis cerebral encontrada en geriatría, vértigo epiléptico atribuible a trauma craneal, y para encefalopatías metabólicas.

Los métodos de esta invención incluyen la administración sistémica del polimorfo Forma III, preferiblemente en forma de una especialidad farmacéutica. En el presente trabajo "administración sistémica" incluye tanto la administración oral como la parenteral. Para la administración oral, algunos compuestos farmacéuticos aceptables incluyen polvos, gránulos, pastillas, tabletas y cápsulas, así como líquidos, jarabes, suspensiones y emulsiones. Estos compuestos pueden también incluir saborizantes, preservativos, agentes de suspensión, espesantes y emulsificantes, así como otros aditivos farmacéuticos aceptables. Para administración parenteral, los compuestos de la presente invención pueden prepararse en soluciones inyectables acuosas que pueden contener buffers, antioxidantes, bacteriostáticos y/u otros aditivos comunmente usados en tales soluciones.

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Los siguientes ejemplos se incluyen a manera ilustrativa, no limitante.

EJEMPLO 1
Síntesis representativa del polimorfo Forma III

El Compuesto 1 (10 g) preparado de acuerdo a los procedimientos de la U.S. Patent N° 6,399,621 (incorporada al presente documento por vía de referencia) se disolvió en 60 mL de ácido acético. La solución fue luego filtrada y calentada a 70-75°C. Agua (70 mL) y carbono (Darco G-60, 5 mg) se agregaron a la solución calentada y la solución resultante se enfrió 5°C cada 30 minutos. A 55°C comenzó la cristalización y se mantuvo estable la temperatura por 30 minutos. La mezcla fue entonces enfriada a 40-45°C y se agregaron 40 mL de agua. La mezcla se enfrió más hasta 25°C en un período de 1 hora y el sólido resultante se filtró y lavó con 40 mL de agua y luego secada para producir 9 g de polimorfo Forma III en forma de un sólido de color amarillo pálido (ver las Figuras 1 y 2 para ver la caracterización del polimorfo Forma III por DSC y difracción de Rayos-X por polvo).

EJEMPLO 2
Síntesis representativa del polimorfo Forma III

El Compuesto 1 (10 g) preparado de acuerdo a los procedimientos de la U.S. Patent N° 6,399,621 fue disuelto en 60 mL de ácido acético. La solución fue luego filtrada y calentada a 70-75°C. Se agregó agua (70 mL) a la solución caliente. Luego de enfriar hasta 67°C se agregaron cristales semilla de polimorfo Forma III (obtenidos por el procedimiento descrito en el Ejemplo 1 anterior) y la mezcla se enfrió a 50°C en dos horas. Se agregaron 40 mL de agua y se llevó la mezcla a temperatura ambiente. El sólido resultante fue filtrado y lavado con 40 mL de agua para producir 9 g de polimorfo Forma III en la forma de un sólido de color amarillo pálido (con endotermo pico DSC en 191,86°C).

EJEMPLO 3
Síntesis representativa del polimorfo Forma III

Se preparó el Compuesto 1 (10 g) de acuerdo a los procedimientos de la U.S. Patent N° 6,399,621 y se disolvió en 60 mL de ácido acético. La solución fue seguidamente filtrada y calentada a 70-75°C. Se agregó agua (70 mL) a la solución caliente. Después de enfriarla a 52°C se agregaron cristales semilla de polimorfo Forma III (obtenidos por el procedimiento descrito en el Ejemplo 1) y se revolvió la mezcla por 30 minutos. Se enfrió la mezcla a 47°C en un período de 30 minutos seguidos de la adición de 40 mL de agua. Después de enfriar la mezcla a la temperatura ambiente, se filtró el sólido resultante y se lavó con 40 mL de agua para obtener 9 g de polimorfo Forma III en forma de un sólido color amarillo pálido (con pico endotérmico DSC en 191,68°C).

EJEMPLO 4 Interconversión del Compuesto 1

Se efectuaron experimentos de interconversión para evaluar la estabilidad termodinámica del Compuesto 1 a temperatura ambiente. Se prepararon tres suspensiones (*slurries*) partiendo de soluciones isopropanol saturadas del Compuesto 1, filtrando las soluciones a través de filtros de 0,2µm y luego agregando una cantidad (en forma de cristales) de una forma polimórfica del Compuesto 1. A la primera suspensión se le agregaron cantidades iguales (unos 25 mg de cada uno) del polimorfo Forma II y del polimorfo Forma III; a la segunda suspensión (*slurry*) se le agregaron cantidades iguales (unos 25 mg de cada uno) del polimorfo Forma I y del polimorfo Forma III; y a la tercera suspensión (*slurry*) se le agregaron aproximadamente 25 mg del polimorfo Forma III. Seguidamente los slurries fueron agitados durante 16 días. Los sólidos resultantes fueron recolectados por filtración en vacío, secados al aire y analizados usando XRPD. Mediante la técnica descrita, la primera suspensión (*slurry*), sembrado con polimorfos Forma I y III, produjo exclusivamente polimorfo Forma III. Por otra parte, la segunda suspensión (*slurry*),

sembrado con polimorfos Forma I y III produjo polimorfo Forma III como producto predominante con apenas una cantidad menor de polimorfo Forma I. La tercera suspensión (*slurry*), sembrado con polimorfo Forma III solamente, produjo polimorfo Forma III exclusivamente. Estos resultados indican que el Compuesto 1, cuando está en forma de suspensión (*slurry*), se convertirá al polimorfo Forma III cuando sea sembrado con cristales del mismo, y bajo esas condiciones será el polimorfo favorecido.

Lo anterior es una descripción detallada de presentaciones particulares de la invención. Debe apreciarse que aunque se han descrito presentaciones específicas de la invención con el propósito de ilustrar, es posible hacer diversas modificaciones sin apartarse del espíritu y alcance de la invención. En consecuencia, la invención no está limitada sino por las reivindicaciones anexas.

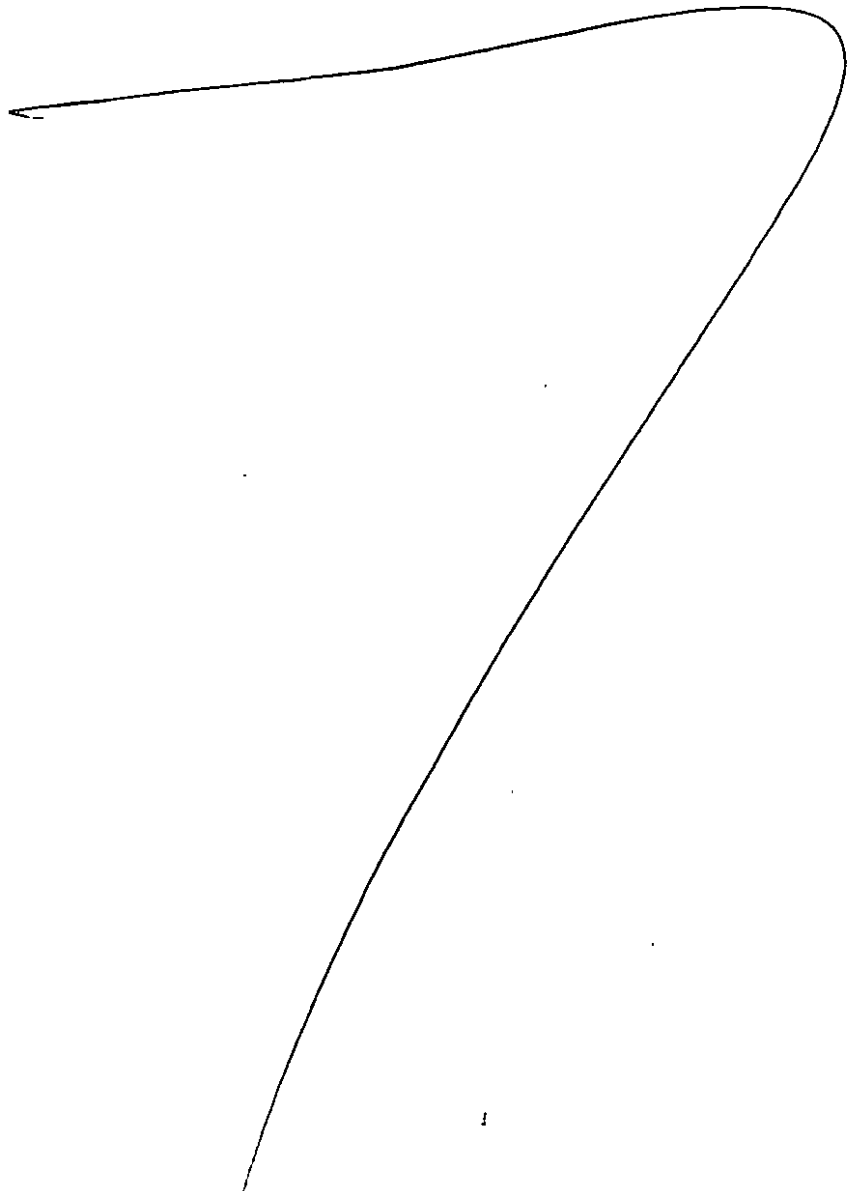
REINVINDICACIONES

Reinvindicamos:

1. El polimorfo Forma III de N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl} fenil)acetamida.
2. El polimorfo Forma III de la reivindicación 1 en el cual el polimorfo presenta un endotermo predominante alrededor de los 191°C medidos con un Calorímetro de Muestreo Diferencial Modulado – *Modulated Differential Scanning Calorimeter* (DSC, siglas en inglés), modelo TA 2920, a una rata de muestreo de 10°C por minuto.
3. El polimorfo Forma III de la reivindicación 1 en el cual el polimorfo presenta un patrón de difracción de rayos-X por polvo con picos característicos expresados en grados 2θ ($\pm 0,2^\circ \theta$) a 18.9 y 28.1.
4. El polimorfo Forma III de la reivindicación 3 en el cual el polimorfo presenta un pico característico adicional expresado en grados 2θ ($\pm 0,2^\circ \theta$) a 10.2.
5. El polimorfo Forma III de la reivindicación 4 en el cual el polimorfo presenta picos característicos adicionales expresados en grados 2θ ($\pm 0,2^\circ \theta$) a 13.3, 20.7, 22.2 y 30.8.
6. El polimorfo Forma III de la reivindicación 1 donde el polimorfo presenta patrón de difracción de rayos-X por polvo como el que muestra la Figura 2.
7. El polimorfo Forma III de la reivindicación 1 donde el polimorfo presenta a los 150°K un análisis cristalográfico por rayos-X de un solo cristal que se muestra a continuación:

Grupo Espacial	$P2_1/n$
$a, \text{\AA}$	9.5887(3)

b , Å	10.3985(4)
c , Å	17.5807(7)
α	90
β	96,8044(14)
γ	90
Z (moléculas/celda unitaria)	4
Densidad calculada (g/cm)	1.436
Temperatura (K)	150



8. El polimorfo Forma III de la reivindicación 1 donde el polimorfo presenta un espectro de FT Infrarrojo Raman como se muestra en la Figura 3.
9. El polimorfo Forma III de la reivindicación 1 donde el polimorfo contiene menos de 2% en peso de impurezas totales, menos de 1% en peso de agua y menos de 0,5% en peso de solvente orgánico.
10. El polimorfo Forma III de la reivindicación 1 donde el polimorfo contiene menos de 1% en peso de impurezas totales, menos de 0,75% en peso de agua y menos de 0,4% en peso de solvente orgánico residual.
11. Un compuesto que comprende el polimorfo Forma III del N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida.
12. El compuesto de la reivindicación 11, que comprende además el N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida en una forma cristalina, de solvato o amorfa distinta del polimorfo Forma III.
13. El compuesto de la reivindicación 11 comprendiendo además el polimorfo Forma I.
14. El compuesto de la reivindicación 11 comprendiendo además el polimorfo Forma II.
15. Un compuesto que comprende el polimorfo Forma III del N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida en combinación con un portador farmacéuticamente aceptable.
16. El compuesto de la reivindicación 15 en el cual el compuesto está formulado para administración oral.
17. El compuesto de la reivindicación 16 en el cual el compuesto está en forma de pastilla, cápsula o tableta.

18. El compuesto de la reivindicación 15 en el cual el polimorfo Forma III está presente en la pastilla, cápsula o tableta en forma de dosis unitaria en una cantidad entre 0,1 y 250 mg.
19. Un compuesto que comprende (a) el polimorfo Forma III del N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida ("Compuesto 1") y (b) una forma cristalina, de solvato, amorfa u otra del Compuesto 1 distinta al polimorfo Forma III, en el cual el peso total del Compuesto 1 en el compuesto es la suma de (a) más (b).
20. El compuesto de la reivindicación 19 el cual comprende menos del 0,1% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
21. El compuesto de la reivindicación 19 el cual comprende menos del 0,5% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
22. El compuesto de la reivindicación 19 el cual comprende menos del 1% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
23. El compuesto de la reivindicación 19 el cual comprende menos del 2% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
24. El compuesto de la reivindicación 19 el cual comprende menos del 5% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
25. El compuesto de la reivindicación 19 el cual comprende menos del 10% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.

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26. El compuesto de la reivindicación 19 el cual comprende menos del 20% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
27. El compuesto de la reivindicación 19 el cual comprende menos del 30% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
28. El compuesto de la reivindicación 19 el cual comprende menos del 40% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
29. El compuesto de la reivindicación 19 el cual comprende menos del 50% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
30. El compuesto de la reivindicación 19 el cual comprende al menos el 50% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
31. El compuesto de la reivindicación 19 el cual comprende al menos el 60% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
32. El compuesto de la reivindicación 19 el cual comprende al menos el 70% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
33. El compuesto de la reivindicación 19 el cual comprende al menos el 80% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.

34. El compuesto de la reivindicación 19 el cual comprende al menos el 90% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
35. El compuesto de la reivindicación 19 el cual comprende al menos el 95% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
36. El compuesto de la reivindicación 19 el cual comprende al menos el 97% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
37. El compuesto de la reivindicación 19 el cual comprende al menos el 98% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
38. El compuesto de la reivindicación 19 el cual comprende al menos el 99% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
39. El compuesto de la reivindicación 19 el cual comprende al menos el 99,5% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
40. El compuesto de la reivindicación 19 el cual comprende al menos el 99,9% en peso del polimorfo Forma III en relación con el peso total del Compuesto 1 en el compuesto.
41. El compuesto de la reivindicación 19 el cual está en forma de pastilla, cápsula o tableta.
42. El compuesto de la reivindicación 19 el cual está en forma de suspensión (*slurry*).

43. Un método para tratar el insomnio en un paciente con tal necesidad, que comprende la administración al paciente de una cantidad efectiva del compuesto de la reivindicación 15.
44. Un método para inducir sueño en un paciente con tal necesidad, que comprende la administración al paciente de una cantidad efectiva del compuesto de la reivindicación 15.
45. Un método para inducir sedación o hipnósis en un paciente con tal necesidad, que comprende la administración al paciente de una cantidad efectiva del compuesto de la reivindicación 15.
46. Un método para inducir relajación en los músculos asociados al esqueleto en un paciente con tal necesidad, que comprende la administración al paciente de una cantidad efectiva del compuesto de la reivindicación 15.

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RESUMEN DE LA DIVULGACIÓN

Polimorfo Forma III del N-metil-N-(3-{3-[2-tienilcarbonil]-pirazol-[1,5- α]-pirimidina-7-yl}fenil)acetamida, y su uso como sedante-hipnótico, ansiolítico, anticonvulsivante, y/o agente relajante de los músculos asociados al esqueleto. Tambien se divulgan compuestos relacionados y métodos, particularmente en cuanto al tratamiento del insomnio.

PATENT COOPERATION TREATY

es

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Dr.-Ing. H. Kinkeldey et al.
Maximilianstr. 58
D-80538 München
ALLEMAGNE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

Date of mailing
(day/month/year)

08-04-2004

Applicant's or agent's file reference

PCT2054KG904gw

IMPORTANT NOTIFICATION

International application No.

PCT/US03/26870

International filing date (day/month/year)

26/08/2003

Priority date (day/month/year)

26/08/2002

Applicant

NEUROCRINE BIOSCIENCES, INC.

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

26/03/2004

2. This date of receipt is:



the actual date of receipt of the demand by this Authority (Rule 61.1(b)).



the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).



the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

- 3.



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



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

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

Name and mailing address of the IPEA/



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

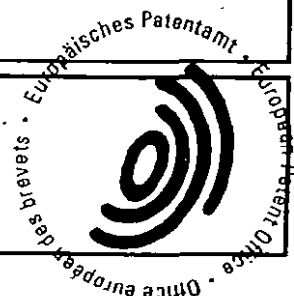
Authorized officer

CHURCHER G

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

(05/04/2004)



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Dr.-Ing. H. Kinkeldey et al.
Maximilianstr. 58
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ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 08/04/2004

Applicant's or agent's file reference

PCT2054KG904gw

IMPORTANT NOTIFICATION

International application No.

PCT/US03/26870

International filing date (day/month/year)

26/08/2003

Priority date (day/month/year)

26/08/2002

Applicant

NEUROCRINE BIOSCIENCES, INC.

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

4. REMINDER

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

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

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

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

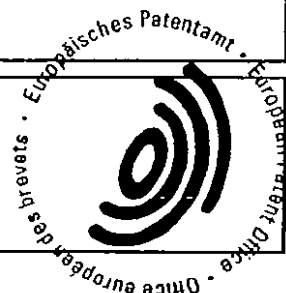
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Form PCT/IPEA/416 (August 2002) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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

Applicant's or agent's file reference PCT2054KG904gw	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/26870	International filing date (day/month/year) 26/08/2003	Priority date (day/month/year) 26/08/2002
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant NEUROCRINE BIOSCIENCES, INC.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

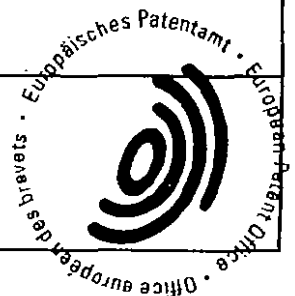
These annexes consists of a total of 1 sheets.

- This report contains indications relating to the following items:

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

Date of submission of the demand 26/03/2004	Date of completion of this report 05/04/2004
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/US03/26870

I. Basis of the report

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

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

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

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

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 690068.569PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/US 03/26870	International filing date (day/month/year) 26/08/2003	(Earliest) Priority Date (day/month/year) 26/08/2002
Applicant NEUROCRINE BIOSCIENCES, INC.		

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 4 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

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

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/26870

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/519 A61P25/00 //(C07D487/04,239:00,
231:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/107256 A1 (O'DONNELL PATRICK B ET AL) 8 August 2002 (2002-08-08) cited in the application claims -----	1,15, 43-46



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

21 November 2003

Date of mailing of the international search report

05/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/26870

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

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

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

Although claims 43 - 46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

- ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/26870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002107256 A1	08-08-2002	US 6384221 B1	07-05-2002
		US 2003199524 A1	23-10-2003



US 20020107256A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2002/0107256 A1

Thiele et al.

(43) Pub. Date:

Aug. 8, 2002

(54) POLYMORPHS OF N-METHYL-N-(3-PHENYL)ACETAMIDE AND COMPOSITIONS AND METHODS RELATED THERETO

Publication Classification

(51) Int. Cl.⁷ A61K 31/519; C07D 487/04

(52) U.S. Cl. 514/262.1; 544/262

(75) Inventors: William J. Thiele, San Diego, CA (US); Patrick B. O'Donnell, San Diego, CA (US)

(57)

ABSTRACT

Polymorphs of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), and use of the same as a sedative-hypnotic, anxiolytic, anticonvulsant, and skeletal muscle relaxant agent. Processes for making the same, as well as related compositions and methods are also disclosed, particularly with regard to treatment of insomnia. A polymorph Form I possessing exception physical and heat stability is provided. A polymorph Form II

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(21) Appl. No.: 09/982,524

(22) Filed: Oct. 16, 2001

Related U.S. Application Data

(63) Continuation of application No. 09/654,447, filed on Sep. 1, 2000

(60) Provisional application No. 60/304,205, filed on Oct. 19, 1999, now abandoned. Provisional application No. 60/229,352, filed on Sep. 2, 1999, now abandoned.

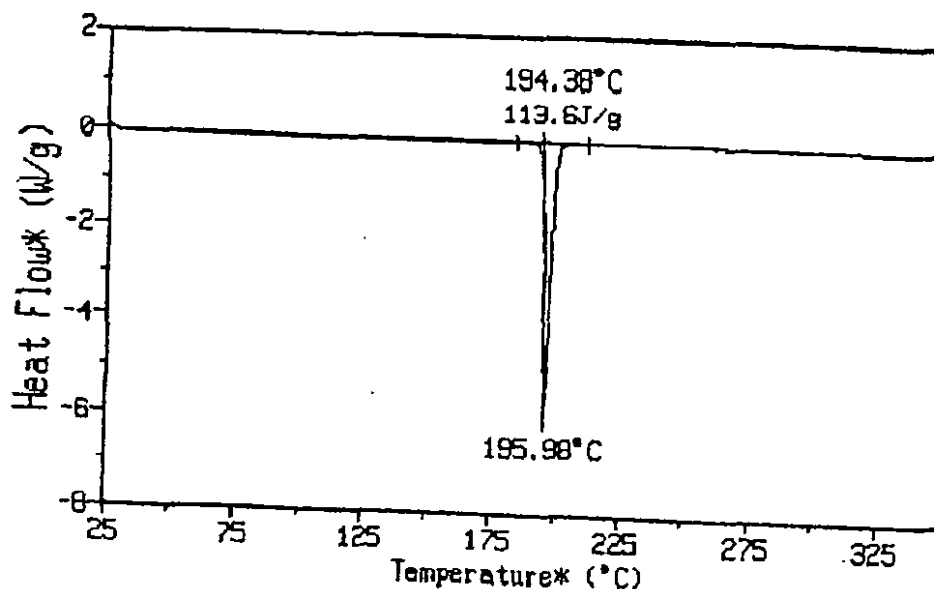
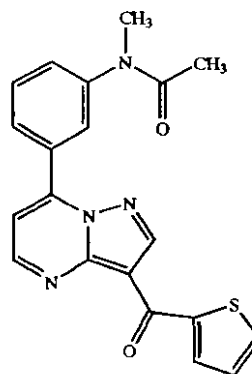


Figure 1

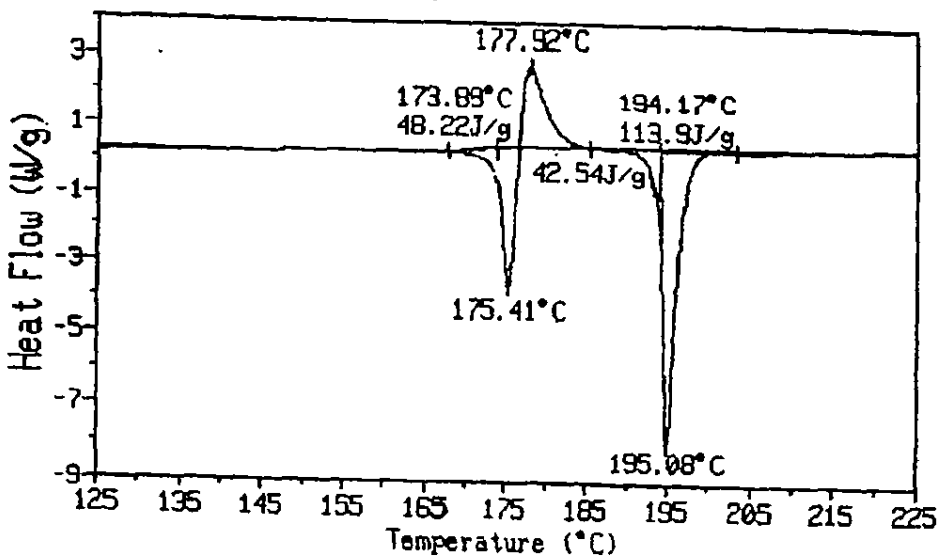


Figure 2

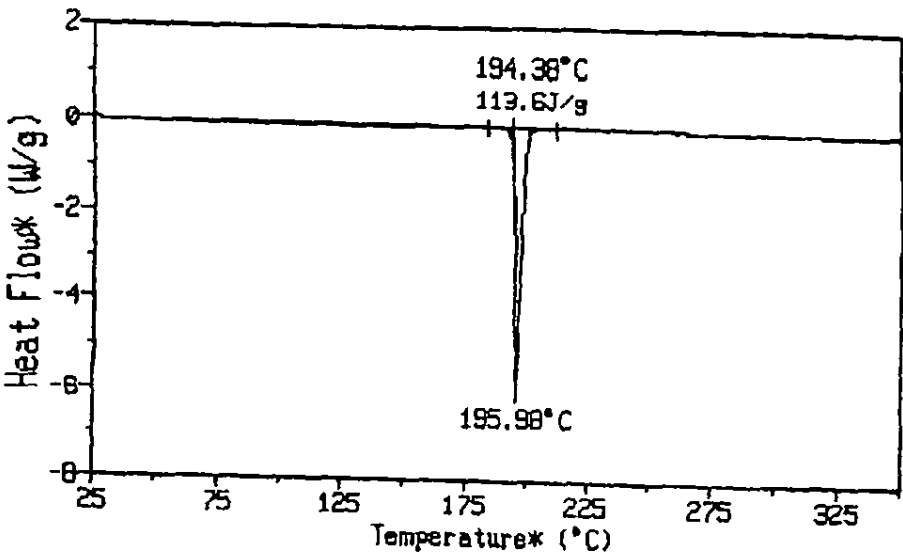


Figure 3

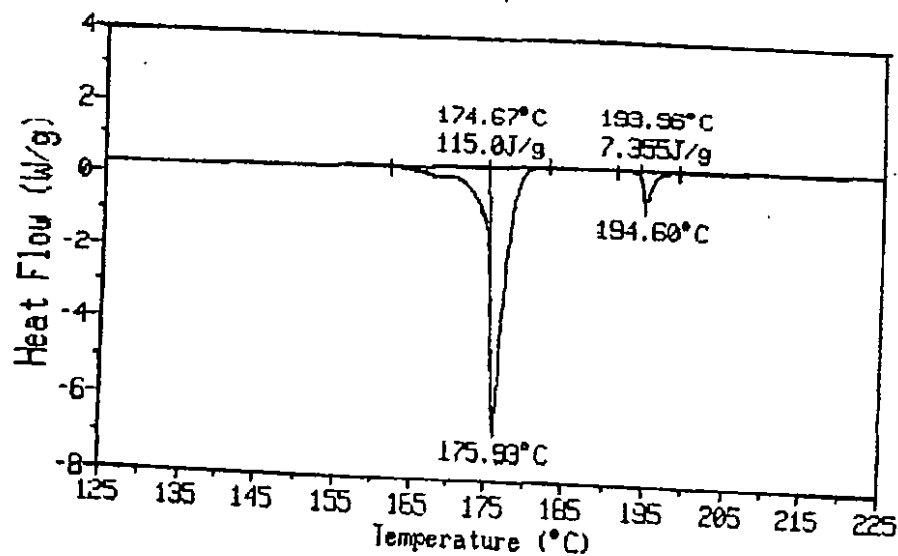


Figure 4

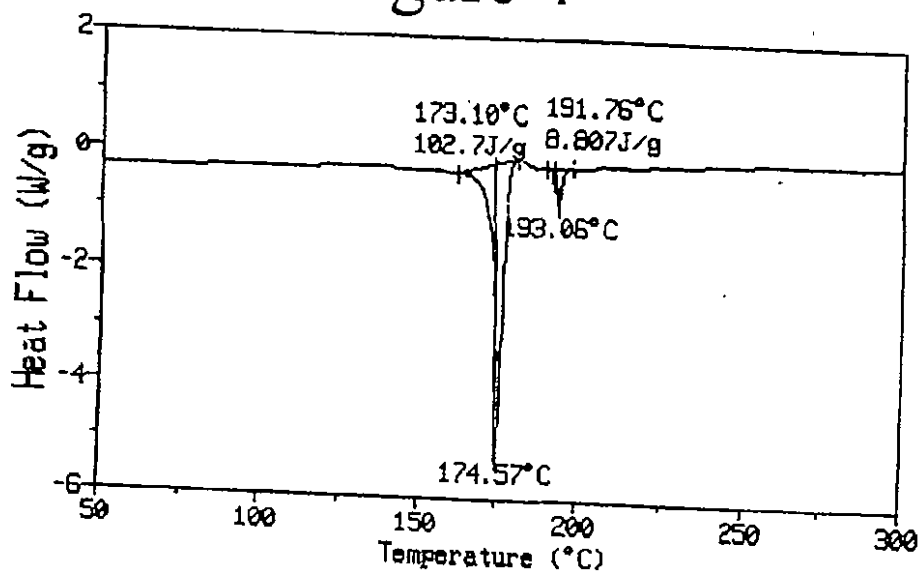


Figure 5

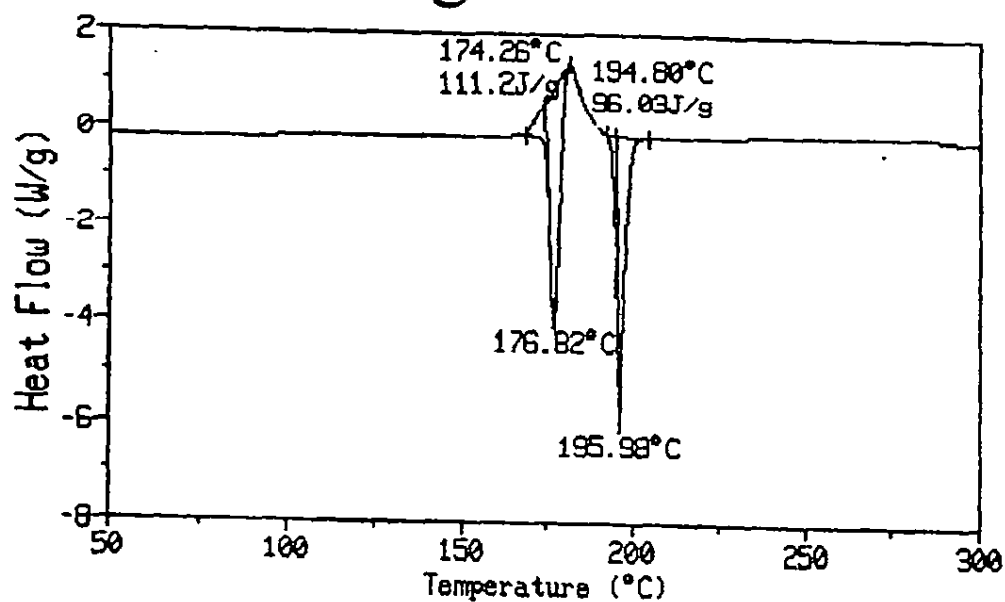


Figure 6

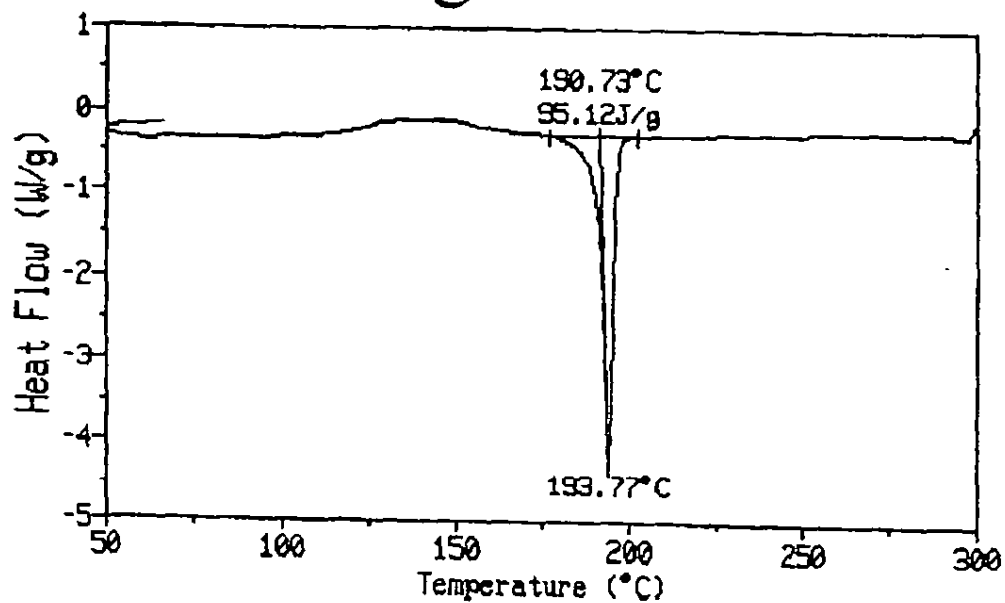


Figure 7

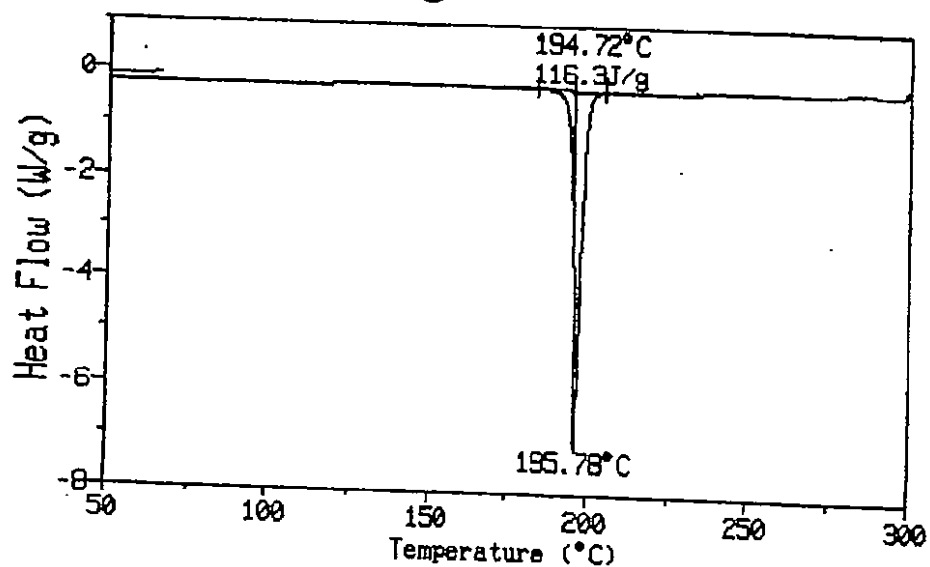


Figure 8

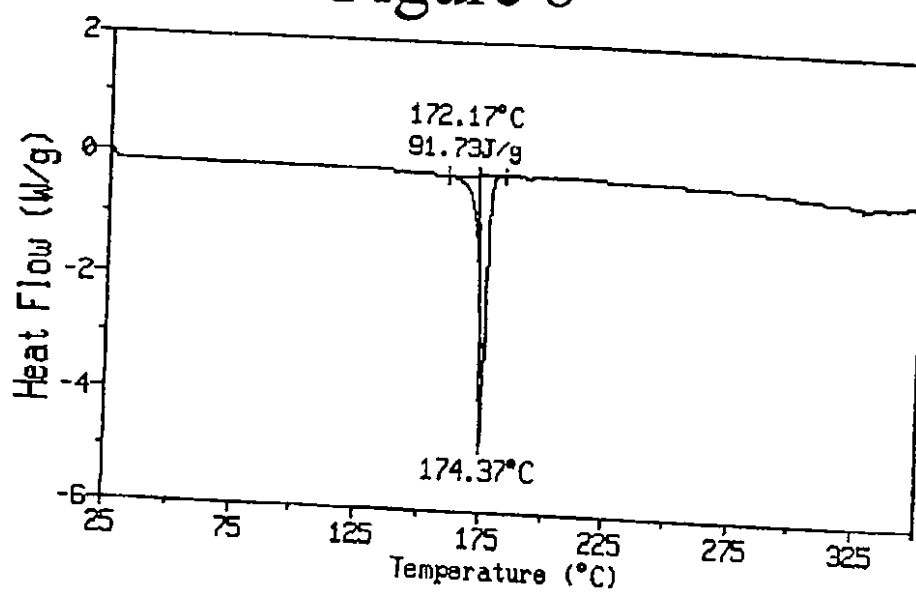
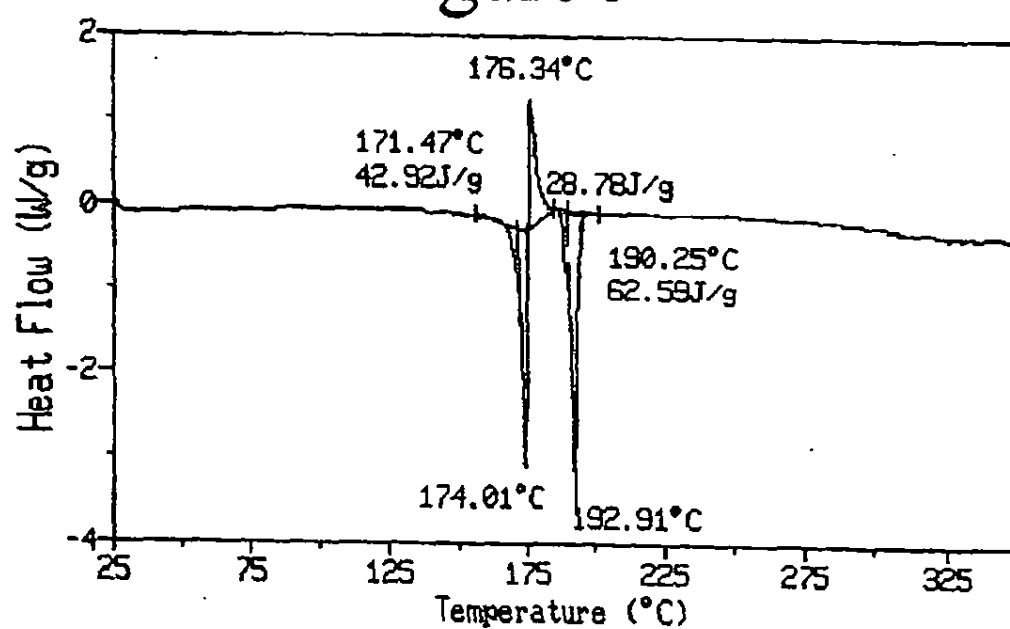


Figure 9



POLYMORPHS OF N-METHYL-N-(3-PHENYL)ACETAMIDE AND COMPOSITIONS AND METHODS RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. patent application Ser. No. 09/421,620 filed Oct. 19, 1999, which application was converted to U.S. Provisional Application for Patent No. 60/(awaiting) by petition on August, 2000, and of U.S. patent application Ser. No. 09/389,524, filed Sep. 2, 1999 which application was converted to U.S. Provisional Application for Patent No. 60/(awaiting) by petition on August, 2000.

FIELD OF THE INVENTION

[0002] This invention is directed to polymorphs of N-methyl-N-(3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl)phenyl)acetamide having activity over a wide range of indications, and particularly useful for the treatment of insomnia, and to related processes, compositions and methods.

BACKGROUND OF THE INVENTION

[0003] The term "insomnia" is used to describe all conditions related to the perception of inadequate or non-restful sleep by the patient (Dement, *International Pharmacopsychiatry* 17:3-38, 1982). Insomnia is the most frequent complaint, being reported by 32% of the adult population surveyed in the Los Angeles area (Bixler et al., *Amer. Journal of Psychiatry* 136:1257-1262, 1979), and 13% of the population surveyed in San Marino, Italy (Lugaresi et al., *Psychiatric Annals* 17:446-453, 1987). Fully 45% of the surveyed adult population of Alachua County, Fla., reported trouble getting to sleep or staying asleep (Karacan et al., *Social Science and Medicine* 10:239-244, 1976). The prevalence of insomnia has also been shown to be related to the age and sex of the individuals, being higher in older individuals and in females.

[0004] Insomnia, if left untreated, may result in disturbances in metabolism and overall body function. Reduced productivity and significant changes in mood, behavior and psychomotor function. Chronic insomnia is associated with a higher incidence of morbidity and mortality. Traditionally, the management of insomnia includes treatment and/or mitigation of the etiological factors, improving sleep hygiene and the administration of hypnotic agents. The early hypnotic agents, such as barbiturates, while effective, elicited a spectrum of unwanted side effects and longer-term complications. For example, barbiturates have the potential to result in lethargy, confusion, depression and a variety of other residual effects many hours post dosing, as well as having a potential for being highly addictive.

[0005] During the 1980's, the pharmaceutical treatment of insomnia shifted away from barbiturates and other CNS depressants toward the benzodiazepine class of sedative-hypnotics. This class of sedative-hypnotic agents showed substantial effectiveness in producing a calming effect which results in sleep-like states in man and animals (Gee et al., *Drugs in Central Nervous Systems*, Horwell (ed.), New York, Marcel Dekker, Inc., 1985, p. 123-147) and had a greater safety margin than prior hypnotics, barbiturates or

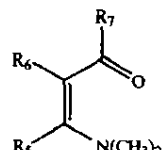
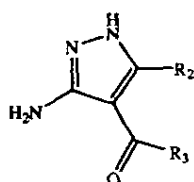
chloral hydrate (Cook and Sepinwall, *Mechanism of Action of Benzodiazepines*, Costa and Greengard (eds.), New York, Raven Press, 1975, p. 1-28). The therapeutic action of benzodiazepines is believed to be mediated by binding to a specific receptor on benzodiazepine GABA complexes in the brain. As a result of this binding, synaptic transmission is altered at neurons containing the benzodiazepine GABA complex (Clody et al., *Benzodiazepines II*, Rechtschaffen and Kales (eds.), New York, Springer-Verlag, 1989, p. 341-354). The clinical usefulness of different benzodiazepine hypnotics relates largely to their pharmacokinetic differences with regard to this binding and, in particular, to the half-lives of the parent compound and its active metabolites (Finkle, *Benzodiazepines II*, Rechtschaffen and Kales (eds.), New York, Springer-Verlag, 1989, p. 619-628).

[0006] As with barbiturates, however, many benzodiazepines also possess side effects that limit their usefulness in certain patient populations. These problems include synergy with other CNS depressants (especially alcohol), the development of tolerance upon repeat dosing, rebound insomnia following discontinuation of dosing, hangover effects the next day, and impairment of psychomotor performance and memory (Cook and Sepinwall, supra; Hartman, *Benzodiazepines II*, Rechtschaffen and Kales (eds.), New York, Springer-Verlag, 1989, p. 187-198; Linnoila and Ellinwood, *Benzodiazepines II*, Rechtschaffen and Kales (eds.), New York, Springer-Verlag, 1989, p. 601-618). Memory impairment, which can include amnesia for events occurring prior to and after drug administration, is of particular concern in the elderly whose cognitive function may already be impaired by the aging process (Ayd, *Benzodiazepines II*, Rechtschaffen and Kales (eds.), New York, Springer-Verlag, 1989, p. 593-600; Finkle, supra; Linnoila and Ellinwood, supra).

[0007] More recently, a new class of agents have undergone development. These agents are non-benzodiazepine compounds, which bind selectively to a specific receptor subtype of the benzodiazepine receptor. This receptor selectivity is thought to be the mechanism by which these compounds are able to exert a robust hypnotic effect, while also demonstrating an improved safety profile relative to the non-selective, benzodiazepine class of agents. The first of these agents to be approved by the United States Food and Drug Administration (FDA) for marketing in the United States was Ambien (zolpidem tartrate), which is based on the imidazopyridine backbone (see U.S. Pat. Nos. 4,382,938 and 4,460,592). In addition to Ambien, another compound known as Sonata (zaleplon), which is a pyrazolopyrimidine-based compound, recently received FDA approval (see U.S. Pat. No. 4,626,538). Other non-benzodiazepine compounds and/or methods for making or using the same have also been reported (see, e.g., U.S. Pat. Nos. 4,794,185, 4,808,594, 4,847,256, 5,714,607, 4,654,347; 5,891,891).

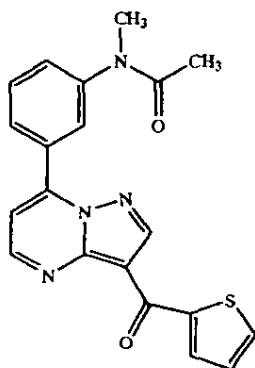
[0008] While significant advances have been made in this field, there is still a need in the art for compounds that are effective as sedative or hypnotic agents generally, particularly in the context of treating insomnia. One such class of compound is disclosed in U.S. Pat. Nos. 4,521,422 and 4,900,836. These patents, particularly U.S. Pat. No. 4,521,422, disclose a genus encompassing certain aryl and heteroaryl[7-(aryl and heteroaryl)-pyrazolo[1,5-a]-pyrimidin-3-yl]methanones. More specifically, U.S. Pat. No. 4,521,422 discloses that compounds of this genus may be made by

reacting an appropriately substituted pyrazole (a) with an appropriately substituted 3-dimethylamino-2-propen-1-one (b).



[0009] One particular compound that falls within the genus of U.S. Pat. No. 4,521,422 is N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide, which has the following structure 1 (referred to herein as "Compound 1"):

Compound 1



[0010] Compound 1 may be made according to the procedures disclosed in U.S. Pat. No. 4,521,422, which procedure is more specifically disclosed in Example 1. In short, Compound 1 is made by reacting an appropriately substituted pyrazole (a) (i.e., wherein R_2 is hydrogen and R_3 is 2-thienyl) with an appropriately substituted 3-dimethylamino-2-propen-1-one (b) (i.e., wherein R_5 and R_6 are hydrogen and R_7 is 3-N(CH₃)(COCH₃)phenyl), followed by recrystallization from dichloromethane/hexane. As one skilled in this field will recognize, the dichloromethane has been used to selectively solubilize or extract Compound 1 away from unwanted impurities, while subsequent addition of hexane causes Compound 1 to crystallize or "crash out." When made in this manner, Compound 1 exists as a mixture of polymorphs.

[0011] While Compound 1 has proven particularly promising for the treatment of insomnia, improved forms of this compound are desired, particularly with regard to enhanced

solubility, oral bioavailability and/or physical stability. The present invention fulfills this need and provides further related advantages.

SUMMARY OF THE INVENTION

[0012] The present invention is directed to substantially pure polymorphs of Compound 1 (referred to herein as "Form I" and "Form II") which have particularly advantageous properties.

[0013] A substantially pure polymorph Form I of Compound 1 exhibits a predominant endotherm at about 196° C. (192-197° C. as measured by a TA 2920 Modulated Differential Scanning Calorimeter (DSC) at a scan rate of 10° C. per minute), and contains less than about 6% by weight of Form II. Specific embodiments of the substantially pure polymorph Form I contain less than about 2% by weight total impurities, less than about 1% by weight water, and/or less than about 0.5% by weight residual organic solvent. Another embodiment includes substantially pure polymorph Form I containing less than 1% by weight total impurities, less than about 0.75% by weight water, and less than 0.4% by weight residual organic solvent. Other embodiments of the polymorph Form I are described further below.

[0014] A substantially pure polymorph Form II of Compound 1 exhibits a predominant endotherm at about 176° C. (173-177° C. as measured by a TA 2920 Modulated Differential Scanning Calorimeter at a scan rate of 10° C. per minute), and contains less than about 20% by weight of Form I. Specific embodiments of the substantially pure polymorph Form II contain less than about 2% by weight total impurities, less than about 1% by weight water, and less than about 0.5% by weight residual organic solvent. Another embodiment includes substantially pure polymorph Form II containing less than 1% by weight total impurities, less than about 0.75% by weight water, and less than 0.4% by weight residual organic solvent. Other embodiments of the polymorph Form II are described further below.

[0015] The polymorphs Form I and II are useful as sedative or hypnotic agents generally and, more specifically, are useful in the treatment of insomnia. Thus, the present invention is also directed to methods for treating a variety of conditions by administering an effective amount of the polymorph Form I and/or II to an animal or subject in need thereof (referred to herein as a "patient"), typically a warm-blooded animal (including a human). Prior to administration, the administered polymorph is generally formulated as a pharmaceutical composition that contains an effective dosage amount of the polymorph in combination with one (or more) pharmaceutically acceptable carrier(s).

[0016] Conditions that may be treated by the polymorphs of this invention, or a pharmaceutical composition containing a polymorph of this invention, include any disorder or disease that may be improved or ameliorated by administration of a polymorph according to the invention, which possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic, anticonvulsant, and/or skeletal muscle relaxant properties. Such conditions include insomnia specifically, as well as sleep disorders generally and other neurological and psychiatric complaints; anxiety states; vigilance disorders, such as for combating behavioral disorders attributable to cerebral vascular damage and to the cerebral sclerosis encoun-

tered in geriatrics; epileptic vertigo attributable to cranial trauma; and metabolic encephalopathies.

[0017] Other aspects of the invention provide methods of making the polymorphs Form I and Form II are disclosed. In one embodiment, substantially pure Form I of Compound 1 is made by forming a solution of acetone and Compound 1, cooling the solution to result in a crystallized mass, and collecting the crystallized mass to yield substantially pure Form I. In another embodiment, substantially pure Form II of Compound 1 is made by forming a solution of methanol and Compound 1, cooling the homogenous solution to result in a crystallized mass, and collecting the crystallized mass to yield substantially pure Form II. Specific embodiments of the invention include those wherein the solution of Compound 1 further comprises one or more other organic solvents, thereby making a combination homogeneous solution.

[0018] Another aspect of the invention provides a method of converting the polymorph Form II to the polymorph Form I. Specific embodiments of this aspect include: 1) exposing the polymorph Form II to a high energy, such as thermal energy or mechanical energy, process. Such processes include: 1) exposing the polymorph Form II to an elevated temperature for a sufficient period of time to convert the polymorph Form II to the polymorph Form I; 2) milling or grinding the polymorph Form II to form the polymorph Form I; 3) dissolving the polymorph Form II in acetone (or a combination of acetone and one or more other solvents) to form a solution, cooling the solution to form a crystallized mass, and collecting the crystallized mass to yield substantially pure Form I; and/or 4) heating the polymorph Form II above its melting point to form a molten mass, and cooling the molten mass to form the polymorph Form I. This aspect of the invention can also be used to purify lots of polymorph Form I that contain unacceptable amounts of the polymorph Form II by subjecting impure polymorph Form I to one or more of the above-described specific embodiments of this aspect of the invention.

[0019] Compositions are also disclosed containing substantially pure Form I or Form II in combination with a pharmaceutically acceptable carrier. Such compositions may assume a variety of forms, including pills, tablet and capsules for oral administration.

[0020] These and other aspects of this invention will be apparent upon reference to the following detailed description and attached figures. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents is hereby incorporated by reference in its entirety.

BRIEF DESCRIPTION OF THE FIGURES

[0021] FIG. 1 is a Differential Scanning Calorimetry (DSC) thermogram of (Compound 1) as prepared by conventional techniques.

[0022] FIG. 2 is a DSC thermogram of the "high" melting point polymorph of Compound 1, referred to herein as Form I.

[0023] FIG. 3 is a DSC thermogram of the "low" melting point polymorph of Compound 1, referred to herein as Form II.

[0024] FIG. 4 is a DSC thermogram of the substantially pure polymorph Form II.

[0025] FIG. 5 is a DSC thermogram of an impure sample of the polymorph Form II containing a high level of Form I.

[0026] FIG. 6 is a DSC thermogram confirming the complete conversion of the polymorph Form II of FIG. 4 to the polymorph Form I by heating.

[0027] FIG. 7 is a DSC thermogram confirming the complete conversion of the polymorph Form II of FIG. 5 to the polymorph Form I by heating.

[0028] FIG. 8 is a DSC thermogram of the polymorph Form II prior to being exposed to high energy milling.

[0029] FIG. 9 is a DSC thermogram of the Compound 1 of FIG. 8 after the polymorph Form II has been exposed to a single pass of high energy milling.

DETAILED DESCRIPTION OF THE INVENTION

[0030] Solids exist in either amorphous or crystalline forms. In the case of crystalline forms, molecules are positioned in 3-dimensional lattice sites. When a compound recrystallizes from a solution or slurry, it may crystallize with different spatial lattice arrangements, a property referred to as "polymorphism," with the different crystal forms individually being referred to as a "polymorph". Different polymorphic forms of a given substance may differ from each other with respect to one or more physical properties, such as solubility and dissociation, true density, crystal shape, compaction behavior, flow properties, and/or solid state stability. In the case of a chemical substance that exists in two (or more) polymorphic forms, the unstable forms generally convert to the more thermodynamically stable forms at a given temperature after a sufficient period of time. When this transformation is not rapid, the thermodynamically unstable form is referred to as the "metastable" form. In general, the stable form exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. However, the metastable form may exhibit sufficient chemical and physical stability under normal storage conditions to permit its use in a commercial form. In this case, the metastable form, although less stable, may exhibit properties desirable over those of the stable form, such as enhanced solubility or better oral bioavailability.

[0031] In the practice of this invention, two different polymorphs of the Compound 1 have been discovered and methods of their preparation have been developed. It has surprisingly been found that substantially pure polymorphic forms of Compound 1 are particularly advantageous with regard to use of the same as a pharmaceutical agent.

[0032] The present inventors have discovered the polymorph Form I, which has a "high" melting point of about 196° C., and the polymorph Form II, which has a "low" melting point of about 176° C., as measured by a TA 2920 Modulated Differential Scanning Calorimeter (TA Instruments, New Castle, Del.), at a scan rate of 10° C. per minute.

[0033] FIG. 1 is a Differential Scanning Calorimetry (DSC) thermogram (as measured by the instrument noted above) of Compound 1 made according to the prior art (see Example 1). As illustrated in FIG. 1, Compound 1 exhibits endotherms at 175.41° C. and 195.08° C., and an exotherm

at 177.930° C., establishing the presence of both the high melting point, Form I polymorph, and the low melting point, Form II polymorph.

[0034] FIG. 2 is a DSC thermogram of substantially pure polymorph Form I made according to the process of the invention. FIG. 1 is a DSC thermogram of substantially pure polymorphic Form II. As illustrated in FIG. 2, Form I exhibits a predominant endotherm at 195.98° C., while FIG. 3 shows that Form II exhibits a predominant endotherm at 175.93° C. (the minor endotherm at 194.6° C. in FIG. 3 is due to the presence of Form I in an amount of about 6% by weight).

[0035] Depending upon the rate of heating, i.e. the scan rate, at which the DSC analysis is conducted, the calibration standard used, instrument calibration, the relative humidity and upon the chemical purity, the endotherms of the respective Forms I and II may vary by about 0.01-10° C., or about 0-5° C., above or below the endotherms depicted in the drawings. For any given sample, the observed endotherm may also differ from instrument to instrument; however, it will generally be within the ranges defined herein provided the instruments are calibrated similarly.

[0036] The polymorphs Form I and Form II differ in their crystal structure as determined by single-crystal X-ray crystallography. The data relating to the single-crystal X-ray crystallography spectrum for Form I is presented in the following Tables 1-6, as obtained on a Picker four-circle goniostat equipped with a Furnas Monochromator (HOG crystal), modified by addition of stepping motors (Slo-Syn) on each of the four axes, and a fifth motor drives a 20-position filter/attenuator wheel.

TABLE 1

Crystal Parameters of Form I	
Crystal Dimensions were:	0.12 x 0.05 x 0.015 mm.
Space Group:	P1bar
Cell Dimensions (at -160.C.; 630 peaks):	a = 9.148(12) b = 9.381(19) c = 12.254(26) alpha = 95.25(2) beta = 97.56(5) gamma = 117.25(3)
Z (Molecules/cell):	2
Volume:	912.89
Calculated Density:	1.370
Wavelength:	0.71073
Molecular Weight:	376.44
F(000):	392
Linear Absorption Coefficient:	2.005

[0037]

TABLE 2

Fractional Coordinates and Isotropic Thermal Parameters for Form I				
Atom	x	y	z	Biso
S(1)	4836(2)	921(2)	3413(2)	32
C(2)	5144(8)	1169(9)	2068(6)	32
C(3)	6077(8)	2759(10)	1966(6)	33
C(4)	6616(7)	3861(8)	3004(6)	21
C(5)	6063(7)	3036(7)	3886(6)	20
C(6)	6208(7)	3615(8)	5088(6)	18
O(7)	5357(5)	2619(6)	5672(4)	30

TABLE 2-continued

Fractional Coordinates and Isotropic Thermal Parameters for Form I				
Atom	x	y	z	Biso
C(8)	7312(7)	5328(8)	5645(5)	19
C(9)	7089(7)	5950(8)	6673(6)	21
N(10)	8255(6)	7498(7)	7116(4)	20
N(11)	9300(6)	7916(6)	6339(4)	16
C(12)	10768(7)	9407(8)	6460(6)	17
C(13)	11659(7)	9532(8)	5616(6)	20
C(14)	11104(8)	8186(9)	4734(6)	22
N(15)	9700(6)	6762(7)	4626(5)	22
C(16)	8790(8)	6629(8)	5438(6)	18
C(17)	11234(8)	10723(7)	7419(6)	18
C(18)	10044(8)	11010(9)	7893(6)	26
C(19)	10561(8)	12267(9)	8784(7)	37
C(20)	12266(8)	13287(9)	9266(6)	33
C(21)	13451(8)	13008(9)	8797(6)	26
C(22)	12967(7)	11748(8)	7883(6)	20
N(23)	9232(8)	12362(9)	9356(6)	51
C(24)	8642(9)	11274(9)	10235(6)	31
C(25)	8492(12)	13108(11)	9028(8)	57
O(26)	7218(6)	13030(6)	9441(4)	36
C(27)	9108(9)	14189(9)	8095(7)	31
H(1)	470*	31*	148*	45
H(2)	643*	313*	128*	44
H(3)	732*	500*	310*	34
H(4)	621*	532*	704*	41
H(5)	1265*	1051*	562*	32
H(6)	1174*	834*	415*	36
H(7)	890*	1034*	758*	39
H(8)	1267*	1419*	986*	43
H(9)	1462*	1365*	908*	43
H(10)	1379*	1161*	757*	34
H(11)	873*	1190*	1091*	46
H(12)	754*	1044*	997*	46
H(13)	938*	1082*	1034*	46
H(14)	1005*	1416*	787*	40
H(15)	820*	1376*	748*	40
H(16)	938*	1525*	840*	40

Notes:
1) Fractional coordinates are X 10⁻⁴ for non-hydrogen atoms and X 10⁻³ for hydrogen atoms. Biso values are X 10.
2) Isotropic values for those atoms refined anisotropically are calculated using the formula given by W. C. Hamilton, Acta Cryst., 12,609 (1959).
3) Parameters marked by an asterisk (*) were not varied.

[0038]

TABLE 3

Bond Distances for Form I		
A	B	Distance
S(1)	C(2)	1.728(9)
S(1)	C(5)	1.763(7)
O(7)	C(6)	1.263(8)
O(26)	C(25)	1.306(12)
N(10)	N(11)	1.392(7)
N(10)	C(9)	1.352(8)
N(11)	C(12)	1.404(7)
N(11)	C(16)	1.415(8)
N(15)	C(14)	1.343(8)
N(15)	C(16)	1.357(9)
N(23)	C(19)	1.514(10)
N(23)	C(24)	1.530(10)
N(23)	C(25)	1.234(9)
C(2)	C(3)	1.365(10)
C(3)	C(4)	1.434(9)
C(4)	C(5)	1.400(10)
C(5)	C(6)	1.490(10)
C(6)	C(8)	1.483(9)
C(8)	C(9)	1.418(9)

TABLE 3-continued

Bond Distances for Form I		
A	B	Distance
C(8)	C(16)	1.421(9)
C(12)	C(13)	1.380(9)
C(12)	C(17)	1.486(9)
C(13)	C(14)	1.428(9)
C(17)	C(18)	1.415(10)
C(17)	C(22)	1.424(8)
C(19)	C(20)	1.409(9)
C(20)	C(21)	1.404(10)
C(21)	C(22)	1.412(9)
C(25)	C(27)	1.584(13)
C(2)	H(1)	.921(7)
C(3)	H(2)	.978(8)
C(4)	H(3)	.945(7)
C(9)	H(4)	.954(7)
C(13)	H(5)	.949(6)
C(14)	H(6)	.961(7)
C(18)	H(7)	.940(6)
C(20)	H(8)	.958(7)
C(21)	H(9)	.952(6)
C(22)	H(10)	.950(7)
C(24)	H(11)	.943(8)
C(24)	H(12)	.939(7)
C(24)	H(13)	.954(7)
C(27)	H(14)	.953(8)
C(27)	H(15)	.942(7)
C(27)	H(16)	.937(8)

[0039]

TABLE 4

Bond Angles for Form I			
A	B	C	Angle
C(2)	S(1)	C(5)	90.8(4)
N(11)	N(10)	C(9)	102.8(5)
N(10)	N(11)	C(12)	124.4(5)
N(10)	N(11)	C(16)	112.7(5)
C(12)	N(11)	C(16)	122.8(6)
C(14)	N(15)	C(16)	115.9(6)
C(19)	N(23)	C(24)	117.0(7)
C(19)	N(23)	C(25)	121.6(10)
C(24)	N(23)	C(25)	120.7(9)
S(1)	C(2)	C(3)	113.1(5)
C(2)	C(3)	C(4)	113.0(7)
C(3)	C(4)	C(5)	111.7(6)
S(1)	C(5)	C(4)	111.3(5)
S(1)	C(5)	C(6)	116.1(5)
C(4)	C(5)	C(6)	132.4(6)
O(7)	C(6)	C(5)	119.4(6)
O(7)	C(6)	C(8)	117.5(7)
C(5)	C(6)	C(8)	123.1(6)
C(6)	C(8)	C(9)	121.6(6)
C(6)	C(8)	C(16)	134.1(6)
C(9)	C(8)	C(16)	104.1(6)
N(10)	C(9)	C(8)	114.9(6)
N(11)	C(12)	C(13)	114.7(6)
N(11)	C(12)	C(17)	120.5(6)
C(13)	C(12)	C(17)	124.8(6)
C(12)	C(13)	C(14)	120.3(6)
N(15)	C(14)	C(13)	124.6(6)
N(11)	C(16)	N(15)	121.7(6)
N(11)	C(16)	C(8)	105.5(6)
N(15)	C(16)	C(8)	132.7(6)
C(12)	C(17)	C(18)	123.3(6)
C(12)	C(17)	C(22)	118.3(6)
C(18)	C(17)	C(22)	118.4(6)
C(17)	C(18)	C(19)	120.5(6)

TABLE 4-continued

Bond Angles for Form I			
A	B	C	Angle
N(23)	C(19)	C(18)	117.8(6)
N(23)	C(19)	C(20)	119.3(7)
C(18)	C(19)	C(20)	122.3(7)
C(19)	C(20)	C(21)	117.4(7)
C(20)	C(21)	C(22)	121.8(6)
C(17)	C(22)	C(21)	119.7(6)
O(26)	C(25)	N(23)	121.1(11)
O(26)	C(25)	C(27)	119.4(8)
N(23)	C(25)	C(27)	119.4(10)
S(1)	C(2)	H(1)	123.1(7)
C(3)	C(2)	H(1)	123.7(9)
C(2)	C(3)	H(2)	124.8(8)
C(4)	C(3)	H(2)	122.0(7)
C(3)	C(4)	H(3)	124.9(7)
C(5)	C(4)	H(3)	123.4(7)
N(10)	C(9)	H(4)	121.8(7)
C(8)	C(9)	H(4)	123.3(7)
C(12)	C(13)	H(5)	120.1(7)
C(14)	C(13)	H(5)	119.7(7)
N(15)	C(14)	H(6)	117.7(7)
C(13)	C(14)	H(6)	117.6(7)
C(17)	C(18)	H(7)	118.4(7)
C(19)	C(18)	H(7)	121.1(7)
C(19)	C(20)	H(8)	124.3(7)
C(21)	C(20)	H(8)	118.2(7)
C(20)	C(21)	H(9)	121.5(7)
C(22)	C(21)	H(9)	116.7(7)
C(17)	C(22)	H(10)	120.2(7)
C(21)	C(22)	H(10)	120.1(6)
N(23)	C(24)	H(11)	110.4(7)
N(23)	C(24)	H(12)	110.3(6)
N(23)	C(24)	H(13)	105.3(7)
H(11)	C(24)	H(12)	111.0(8)
H(11)	C(24)	H(13)	109.7(7)
H(12)	C(24)	H(13)	110.0(7)
C(25)	C(27)	H(14)	111.7(7)
C(25)	C(27)	H(15)	106.5(7)
C(25)	C(27)	H(16)	107.0(8)
H(14)	C(27)	H(15)	109.9(8)
H(14)	C(27)	H(16)	110.4(7)
H(15)	C(27)	H(16)	111.3(7)

[0040]

TABLE 5

Anisotropic Thermal Parameters for Form I (bij form)						
Atom	b11	b22	b33	b12	b13	b23
S(1)	79(3)	80(4)	77(2)	22(3)	-5(2)	-3(2)
C(2)	73(12)	128(15)	60(7)	44(12)	-17(8)	-29(9)
C(3)	86(13)	143(16)	56(7)	32(12)	24(8)	7(9)
C(4)	39(10)	88(13)	34(6)	10(9)	-2(6)	-14(7)
C(5)	50(10)	37(11)	58(7)	19(9)	1(7)	2(7)
C(6)	46(11)	71(12)	46(7)	39(10)	1(7)	16(8)
O(7)	83(8)	96(9)	54(5)	6(7)	5(5)	30(6)
C(8)	63(11)	89(13)	33(6)	38(10)	12(7)	23(7)
C(9)	64(11)	87(13)	45(7)	35(10)	16(7)	34(8)
N(10)	57(9)	91(11)	34(5)	30(8)	8(6)	15(6)
N(11)	53(9)	70(10)	29(5)	26(8)	11(6)	4(6)
C(12)	44(10)	74(12)	40(6)	44(9)	-3(7)	10(7)
C(13)	49(10)	77(12)	42(6)	25(10)	7(7)	12(7)
C(14)	56(10)	111(13)	35(6)	32(10)	19(7)	16(7)
N(15)	57(9)	85(10)	46(6)	31(9)	12(6)	10(6)
C(16)	64(11)	73(12)	29(6)	31(10)	11(7)	2(7)
C(17)	69(11)	45(11)	34(6)	18(9)	-1(7)	0(7)
C(18)	42(10)	118(13)	49(7)	28(10)	-10(7)	-27(8)
C(19)	56(11)	151(16)	92(8)	62(11)	17(8)	-47(10)

TABLE 5-continued

Anisotropic Thermal Parameters for Form I (bij form)						
Atom	b11	b22	b33	b12	b13	b23
C(20)	85(12)	108(14)	62(7)	32(11)	-4(8)	-38(8)
C(21)	63(11)	111(14)	54(7)	47(10)	4(7)	3(8)
C(22)	65(11)	57(11)	48(7)	26(10)	14(7)	15(7)
N(23)	158(14)	162(15)	100(8)	77(13)	-24(9)	-50(9)
C(24)	163(16)	118(15)	50(7)	79(13)	44(8)	43(8)
C(25)	230(23)	143(18)	94(11)	110(17)	-119(13)	-84(11)
O(26)	85(9)	191(12)	66(5)	88(9)	5(6)	-24(6)
C(27)	122(14)	138(15)	60(7)	77(12)	28(8)	41(9)

Form of the anisotropic thermal parameter:
 $\exp[-(h^{**2}b_{11} + k^{**2}b_{22} + l^{**2}b_{33} + 2h^{**}kb_{12} + 2h^{**}lb_{13} + 2klb_{23})]$
All values are $\times 10^{-4}$.

[0041]

TABLE 6

Anisotropic Thermal Parameters for Form I (Uij form)						
Atom	U11	U22	U33	U12	U13	U23
S(1)	25(1)	27(1)	56(2)	7(1)	-3(1)	-1(1)
C(2)	23(4)	44(5)	44(5)	15(4)	-8(4)	-15(4)
C(3)	28(4)	49(5)	40(5)	11(4)	11(4)	3(4)
C(4)	13(3)	30(4)	25(4)	3(3)	-1(3)	-7(4)
C(5)	16(3)	13(4)	42(5)	6(3)	1(3)	1(4)
C(6)	15(4)	24(4)	33(5)	13(3)	1(3)	8(4)
O(7)	27(3)	33(3)	39(3)	2(2)	3(3)	15(3)
C(8)	20(4)	31(4)	24(4)	13(3)	6(3)	11(4)
C(9)	21(4)	30(4)	33(5)	12(3)	8(3)	17(4)
N(10)	18(3)	31(4)	25(4)	10(3)	4(3)	8(3)
N(11)	17(3)	24(3)	21(3)	9(3)	5(3)	2(3)
C(12)	14(3)	25(4)	29(5)	15(3)	-1(3)	5(3)
C(13)	16(3)	26(4)	30(5)	8(3)	3(3)	6(4)
C(14)	18(3)	38(5)	25(5)	11(3)	9(3)	8(4)
N(15)	18(3)	29(4)	33(4)	10(3)	6(3)	5(3)
C(16)	21(3)	25(4)	21(4)	10(3)	5(3)	1(3)
C(17)	22(4)	15(4)	25(4)	6(3)	0(3)	0(3)
C(18)	13(3)	40(5)	35(5)	9(3)	-5(3)	-13(4)
C(19)	18(4)	52(5)	67(6)	21(4)	8(4)	-24(5)
C(20)	27(4)	37(5)	45(5)	11(4)	-2(4)	-19(4)
C(21)	20(4)	38(5)	39(5)	15(3)	2(3)	2(4)
C(22)	21(4)	20(4)	35(5)	9(3)	7(3)	8(4)
N(23)	51(5)	55(5)	73(6)	26(4)	-12(4)	-25(4)
C(24)	53(5)	40(5)	36(5)	26(4)	21(4)	21(4)
C(25)	74(7)	49(6)	68(8)	36(6)	-57(6)	-42(6)
O(26)	27(3)	65(4)	48(4)	29(3)	3(3)	-12(3)
C(27)	39(4)	47(5)	43(5)	25(4)	14(4)	21(4)

Similarly, the data relating to the single-crystal X-ray crystallography spectrum for Form II is presented in the following Tables 7-12.

[0042]

TABLE 7

Crystal Parameters of Form II	
Crystal Dimensions:	.35 x .20 x .12 mm.
Space Group:	P2 ₁ /a1
Cell Dimensions (at -176° C.; 22 reflections):	a = 6.807(5) b = 29.581(19) c = 9.053(6) beta = 99.62(2)
Z (Molecules/cell):	4
Volume:	1797.18
Calculated Density:	1.391

TABLE 7-continued

Crystal Parameters of Form II	
Wavelength:	0.71069
Molecular Weight:	376.44
Linear Absorption Coefficient:	2.037

[0043]

TABLE 8

Fractional Coordinates and Isotropic Thermal Parameters for Form II				
Atom	x	y	z	Biso
S(1)	4378(3)	1289(1)	6595(2)	35
C(2)	5151(12)	794(2)	5925(8)	34
C(3)	6289(12)	869(3)	4840(8)	34
C(4)	6493(11)	1329(3)	4514(7)	26
C(5)	5536(11)	1608(2)	5382(7)	21
C(6)	5313(11)	2094(2)	5514(8)	23
O(7)	4801(8)	2253(2)	6651(5)	35
C(8)	5607(10)	2418(2)	4323(7)	20
C(9)	5589(10)	2878(2)	4557(7)	21
N(10)	5744(8)	3129(2)	3361(6)	21
N(11)	5862(8)	2809(2)	2283(6)	19
C(12)	5963(10)	2903(2)	792(7)	19
C(13)	6030(10)	2539(2)	-105(7)	20
C(14)	5930(10)	2102(2)	485(7)	20
N(15)	5840(9)	2011(2)	1908(6)	20
C(16)	5765(11)	2369(2)	2798(7)	21
C(17)	6018(10)	3376(2)	253(7)	16
C(18)	7129(10)	3711(2)	1090(7)	23
C(19)	7262(11)	4142(2)	459(8)	25
C(20)	6298(11)	4232(2)	-961(8)	24
C(21)	5168(11)	3900(2)	-1767(7)	24
C(22)	5008(11)	3476(2)	-1159(7)	21
N(23)	8335(11)	4496(2)	1368(7)	33
C(24)	7149(12)	4796(3)	2197(9)	42
C(25)	10210(15)	4577(3)	1391(8)	36
O(26)	11062(8)	4913(2)	2093(5)	34
C(27)	11428(11)	4247(3)	569(8)	33
H(1)	484*	50*	626*	44
H(2)	688*	63*	435*	44
H(3)	722*	144*	377*	36
H(4)	548*	301*	550*	31
H(5)	614*	258*	-113*	29
H(6)	593*	185*	-18*	30
H(7)	779*	365*	208*	33
H(8)	641*	452*	-139*	34
H(9)	449*	396*	-275*	34
H(10)	420*	325*	-172*	31
H(11)	761*	477*	324*	52
H(12)	730*	510*	191*	52
H(13)	579*	471*	198*	52
H(14)	1144*	396*	101*	43
H(15)	1085*	423*	-46*	43
H(16)	1276*	435*	65*	43

Note:
1) Fractional coordinates are $\times 10^{-4}$ for non-hydrogen atoms and $\times 10^{-3}$ for hydrogen atoms. Biso values are $\times 10$.
2) Isotropic values for those atoms refined anisotropically are calculated using the formula given by W. C. Hamilton, Acta Cryst. 12:609 (1959)
3) Parameters marked by an asterisk (*) were not varied.

[0044]

TABLE 9

Bond Distances for Form II		
A	B	Distance
S(1)	C(2)	1.703(8)
S(1)	C(5)	1.734(6)
O(7)	C(6)	1.233(7)
O(26)	C(25)	1.267(9)
N(10)	N(11)	1.373(6)
N(10)	C(9)	1.332(7)
N(11)	C(12)	1.391(7)
N(11)	C(16)	1.389(7)
N(15)	C(14)	1.328(7)
N(15)	C(16)	1.336(8)
N(23)	C(19)	1.451(9)
N(23)	C(24)	1.486(8)
N(23)	C(25)	1.295(9)
C(2)	C(5)	1.366(9)
C(3)	C(4)	1.405(9)
C(4)	C(5)	1.377(9)
C(5)	C(6)	1.453(9)
C(6)	C(8)	1.480(8)
C(8)	C(9)	1.379(8)
C(8)	C(16)	1.410(8)
C(12)	C(13)	1.353(8)
C(12)	C(17)	1.484(8)
C(13)	C(14)	1.405(8)
C(17)	C(18)	1.392(8)
C(17)	C(22)	1.379(9)
C(18)	C(19)	1.406(9)
C(19)	C(20)	1.369(9)
C(20)	C(21)	1.379(9)
C(21)	C(22)	1.379(8)
C(25)	C(27)	1.548(10)
C(2)	H(1)	.950(7)
C(3)	H(2)	.950(7)
C(4)	H(3)	.949(6)
C(9)	H(4)	.950(6)
C(13)	H(5)	.950(6)
C(14)	H(6)	.950(6)
C(18)	H(7)	.950(7)
C(20)	H(8)	.950(6)
C(21)	H(9)	.950(7)
C(22)	H(10)	.949(7)
C(24)	H(11)	.952(8)
C(24)	H(12)	.949(8)
C(24)	H(13)	.948(8)
C(27)	H(14)	.952(8)
C(27)	H(15)	.949(8)
C(27)	H(16)	.952(7)

[0045]

TABLE 10

Bond Angles for Form II			
A	B	C	Angle
C(2)	S(1)	C(5)	92.4(4)
N(11)	N(10)	C(9)	102.4(4)
N(10)	N(11)	C(12)	124.7(5)
N(10)	N(11)	C(16)	113.4(5)
C(12)	N(11)	C(16)	121.8(6)
C(14)	N(15)	C(16)	116.0(5)
C(19)	N(23)	C(24)	116.9(7)
C(19)	N(23)	C(25)	123.0(7)
C(24)	N(23)	C(25)	119.9(8)
S(1)	C(2)	C(3)	111.3(6)
C(2)	C(3)	C(4)	113.3(7)
C(3)	C(4)	C(5)	112.9(6)
S(1)	C(5)	C(4)	110.1(5)

TABLE 10-continued

Bond Angles for Form II			
A	B	C	Angle
S(1)	C(5)	C(6)	114.9(5)
C(4)	C(5)	C(6)	135.0(6)
O(7)	C(6)	C(5)	119.6(6)
O(7)	C(6)	C(5)	116.9(6)
C(5)	C(6)	C(8)	123.4(6)
C(6)	C(8)	C(9)	121.4(6)
C(6)	C(8)	C(16)	133.5(6)
C(9)	C(8)	C(16)	104.9(6)
N(10)	C(9)	C(8)	115.0(5)
N(11)	C(12)	C(13)	115.8(6)
N(11)	C(12)	C(17)	121.0(6)
C(13)	C(12)	C(17)	123.1(6)
C(12)	C(13)	C(14)	119.7(6)
N(15)	C(14)	C(13)	124.6(6)
N(11)	C(16)	N(15)	122.1(6)
N(11)	C(16)	C(8)	104.4(6)
N(15)	C(16)	C(8)	133.5(6)
C(12)	C(17)	C(18)	122.3(6)
C(12)	C(17)	C(22)	118.2(6)
C(18)	C(17)	C(22)	119.4(6)
C(17)	C(18)	C(19)	119.4(7)
N(23)	C(19)	C(18)	119.0(7)
N(23)	C(19)	C(20)	120.6(7)
C(18)	C(19)	C(20)	120.3(7)
C(19)	C(20)	C(21)	119.7(6)
C(20)	C(21)	C(22)	120.6(7)
C(17)	C(22)	C(21)	120.4(7)
O(26)	C(25)	N(23)	121.4(8)
O(26)	C(25)	C(27)	119.9(8)
N(23)	C(25)	C(27)	118.7(8)
S(1)	C(2)	H(1)	124.4(7)
C(3)	C(2)	H(1)	124.3(8)
C(2)	C(3)	H(2)	123.3(8)
C(4)	C(3)	H(2)	123.4(8)
C(3)	C(4)	H(3)	123.6(8)
C(5)	C(4)	H(3)	123.5(7)
N(10)	C(9)	H(4)	122.5(7)
C(8)	C(9)	H(4)	122.6(7)
C(12)	C(13)	H(5)	120.1(7)
C(14)	C(13)	H(5)	120.2(6)
N(15)	C(14)	H(6)	117.7(6)
C(13)	C(14)	H(6)	117.7(6)
C(17)	C(18)	H(7)	120.4(7)
C(19)	C(18)	H(7)	120.2(7)
C(19)	C(20)	H(8)	120.1(8)
C(21)	C(20)	H(8)	120.2(8)
C(20)	C(21)	H(9)	119.7(7)
C(22)	C(21)	H(9)	119.7(7)
C(17)	C(22)	H(10)	119.8(7)
C(21)	C(22)	H(10)	119.8(7)
N(23)	C(24)	H(11)	109.2(7)
N(23)	C(24)	H(12)	109.5(7)
N(23)	C(24)	H(13)	109.5(7)
H(11)	C(24)	H(12)	109.4(7)
H(11)	C(24)	H(13)	109.5(8)
H(12)	C(24)	H(13)	109.7(8)
C(25)	C(27)	H(14)	109.5(6)
C(25)	C(27)	H(15)	109.7(7)
C(25)	C(27)	H(16)	109.5(7)
H(14)	C(27)	H(15)	109.4(7)
H(14)	C(27)	H(16)	109.2(8)
H(15)	C(27)	H(16)	109.4(7)

[0046]

TABLE 11

Anisotropic Thermal Parameters for Form II (bij form)						
Atom	b11	b22	b33	b12	b13	b23
S(1)	215(6)	10.5(3)	100(3)	-7(1)	45(4)	14(3)
C(2)	239(28)	7(1)	101(12)	-4(4)	-12(15)	10(3)
C(3)	267(30)	7(1)	92(12)	4(5)	9(16)	4(3)
C(4)	192(23)	9(1)	38(9)	-6(4)	-3(12)	6(3)
C(5)	113(22)	7(1)	55(10)	-9(4)	-9(12)	9(3)
C(6)	111(21)	7(1)	66(10)	-6(4)	5(12)	1(3)
O(7)	292(18)	12(1)	54(7)	-7(3)	74(9)	-5(2)
C(8)	141(22)	6(1)	47(9)	-5(4)	21(11)	-1(2)
C(9)	118(21)	9(1)	35(9)	-5(4)	19(11)	-4(3)
N(10)	149(18)	6(1)	58(8)	0(3)	46(10)	-5(2)
N(11)	110(17)	7(1)	49(8)	-6(3)	34(9)	-5(2)
C(12)	103(21)	6(1)	59(10)	3(4)	23(12)	5(3)
C(13)	145(22)	6(1)	50(9)	-4(4)	63(12)	-3(2)
C(14)	105(22)	7(1)	48(10)	1(4)	2(11)	-4(3)
N(15)	154(18)	4(1)	61(8)	6(3)	32(10)	2(2)
C(16)	120(21)	7(1)	60(10)	1(4)	37(12)	4(3)
C(17)	79(20)	5(1)	54(10)	-4(3)	25(12)	-4(2)
C(18)	163(22)	5(1)	78(10)	-1(4)	45(12)	-3(3)
C(19)	152(23)	6(1)	85(11)	-3(4)	17(13)	1(3)
C(20)	182(24)	4(1)	92(11)	4(4)	79(14)	8(3)
C(21)	168(24)	7(1)	73(11)	-7(4)	62(13)	1(3)
C(22)	126(21)	7(1)	57(10)	4(4)	44(12)	-1(3)
N(23)	185(21)	9(1)	112(11)	4(4)	50(12)	5(3)
C(24)	257(30)	9(1)	153(15)	14(5)	27(17)	-20(3)
C(25)	273(32)	11(1)	76(12)	0(5)	61(17)	17(3)
O(26)	297(19)	6(1)	90(8)	-18(3)	36(10)	-3(2)
C(27)	160(24)	13(1)	89(11)	-11(4)	68(14)	-11(3)

Note: Form of the anisotropic thermal parameter: $\exp[-(h^{**2}b_{11} + (k^{**2}b_{22} + (l^{**2}b_{33} + 2hkb_{12} + 2hkb_{13} + 2klb_{23}))]$
All values are X 10⁻⁴.

[0047]

TABLE 12

Anisotropic Thermal Parameters for Form II (Uij form)						
Atom	U11	U22	U33	U12	U13	U23
S(1)	49(1)	47(1)	41(1)	-7(1)	14(1)	19(1)
C(2)	55(6)	29(5)	41(5)	-4(4)	-4(5)	14(4)
C(3)	61(7)	29(5)	37(5)	4(5)	3(5)	5(4)
C(4)	44(5)	39(5)	15(4)	-6(5)	-1(4)	8(4)
C(5)	26(5)	31(4)	22(4)	-9(4)	-3(4)	12(3)
C(6)	25(5)	33(5)	27(4)	-6(4)	2(4)	2(4)
O(7)	67(4)	51(3)	22(3)	-7(3)	22(3)	-7(3)
C(8)	32(5)	25(4)	19(4)	-5(4)	6(3)	-1(3)
C(9)	27(5)	38(5)	14(4)	-5(4)	6(3)	-5(4)
N(10)	34(4)	25(3)	23(3)	0(3)	14(3)	-7(3)
N(11)	25(4)	30(4)	20(3)	-6(3)	10(3)	-7(3)
C(12)	23(5)	26(4)	24(4)	3(4)	7(4)	6(4)
C(13)	33(5)	26(4)	20(4)	-4(4)	19(4)	-4(3)
C(14)	24(5)	31(5)	19(4)	1(4)	1(3)	-5(4)
N(15)	35(4)	19(3)	25(3)	6(3)	10(3)	3(3)
C(16)	27(5)	31(5)	24(4)	1(4)	11(4)	5(4)
C(17)	18(5)	24(4)	22(4)	-4(3)	7(4)	-6(3)
C(18)	37(5)	21(4)	32(4)	-1(4)	14(4)	-3(4)
C(19)	35(5)	26(5)	34(4)	-3(4)	5(4)	1(4)
C(20)	42(6)	19(4)	37(5)	4(4)	24(4)	11(3)
C(21)	38(5)	30(4)	29(4)	-7(4)	19(4)	1(4)
C(22)	29(5)	31(5)	23(4)	4(4)	13(4)	-1(3)
N(23)	42(5)	41(5)	45(4)	4(4)	15(4)	7(4)
C(24)	59(7)	39(5)	62(6)	14(5)	8(5)	-26(4)

TABLE 12-continued

Anisotropic Thermal Parameters for Form II (Uij form)						
Atom	U11	U22	U33	U12	U13	U23
O(25)	62(7)	47(6)	31(5)	0(5)	18(5)	23(4)
O(26)	68(4)	27(3)	36(3)	-18(3)	11(3)	-4(3)
C(27)	37(6)	58(6)	36(5)	-11(4)	21(4)	-15(4)

Note: Form of the anisotropic thermal parameter: $\exp[-2(\pi^{**2})[(h^{**2}(a^{**2})U_{11} + (k^{**2})(b^{**2})U_{22} + (l^{**2})(c^{**2})U_{33} + 2hk(a^{**}b^{**})U_{12} + 2hl(a^{**}c^{**})U_{13} + 2kl(b^{**}c^{**})U_{23})]]$
All values are X 10⁻³

[0048] As evidenced by the above data, Compound 1 exists as a mixture or blend of polymorphic Forms I and II when made according to prior art techniques. It has been discovered that the above-described Form I is a higher melting, stable polymorph, while the Form II is the lower melting, metastable polymorph. In the context of this invention, Form I is considered to be "substantially pure" when Form II constitutes less than about 6% (by weight), less than about 3%, or less than about 1% of Form I. Form II is considered to be "substantially pure" when Form I constitutes less than about 20% (by weight), less than about 10%, or less than about 5% of Form II. In addition, a substantially pure form of either Form I or Form II will generally contain less than about 2% total impurities, less than about 1% water, and less than about 0.5% residual organic solvent.

[0049] Polymorphic Forms I and II of this invention may be obtained by crystallization, starting from Compound 1, with each polymorph resulting by crystallization from a different solvent. More specifically, Compound 1 may be obtained by the procedure disclosed in U.S. Pat. No. 4,521, 422. Compound 1 is then crystallized from acetone as disclosed in Example 2 to yield Form I. Form II may also be obtained from Compound 1 as set forth above, but by crystallization from methanol as disclosed in Example 3.

[0050] Accordingly, in another embodiment of this invention, a process is disclosed for preparing substantially pure Form I or Form II. The process involves the step of forming a homogeneous solution of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide in acetone (for production of Form I) or methanol (for production of Form II). A homogeneous solution may be formed, for example, by mixing N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide with the appropriate solvent, followed by heating. The homogeneous solution is then cooled, resulting in the crystallization of substantially pure Form I (if the solvent is acetone) or substantially pure Form II (if the solvent is methanol), which crystals are then collected and dried (e.g., at 40° C. for a period of time, such as six or more hours). In order to effect preferential crystallization of one form over the other, the crystallization solvent can be seeded with crystals of the desired polymorph.

[0051] Depending upon the method in which the crystallization is conducted, the polymorph Form II may be obtained by crystallization from solvents such as methanol, acetonitrile, 1-butanol, diethyl ether, N,N-dimethylformamide (DMF), toluene, tetrahydrofuran (THF) and combinations thereof. Similarly, the polymorph Form I may be obtained by crystallization from solvents such as acetone, ethyl acetate, toluene and combinations thereof.

[0052] Large-scale processes of manufacture generally include transfer of a concentrated solution containing a desired compound. Accordingly, the Compound 1 may be added to the crystallization solvent as a solid or as a solution in a cosolvent, such as methylene chloride, methylene chloride/hexane or other organic solvent. The polymorph is then crystallized from acetone or methanol as desired to form the polymorph Form I or Form II, respectively.

[0053] The concentration of Compound 1 present in the cosolvent may vary from 0.1% wt. to saturation, 0.1% wt. to about 16%. The concentration of Compound 1 in the cosolvent will vary according to the temperature at which the cosolvent is held. Generally, warmer temperatures will provide more concentrated solutions of Compound 1.

[0054] A solution containing cosolvent and Compound 1 can be added to the crystallization solvent (for example, methanol or acetone) or the crystallization solvent can be added to the solution containing cosolvent and Compound 1. In either case, the solution containing Compound 1 is generally at ambient temperature or at an elevated temperature with respect to ambient temperature, and the crystallization solvent temperature is independently initially chilled (a temperature below ambient temperature), at ambient temperature, or at an elevated temperature (a temperature above ambient temperature). Alternatively, a solution containing Compound 1 and the cosolvent can undergo a solvent exchange and to form a solution or heterogeneous mixture of the crystallization solvent and Compound 1, as described in Example 4.

[0055] When conducting a crystallization, the crystallization solvent can be seeded with one or more crystals of a particular polymorph in order to promote formation of that particular crystal in the crystallization solvent. Seeding of the crystallization solvent is optional. In one embodiment, Compound 1 is dissolved in hot acetone. After cooling has begun, the crystallization solvent is seeded with crystals of the polymorph Form I. Alternatively, the seed crystals can be added once the crystallization solvent is saturated with Compound 1.

[0056] As used herein, the term "crystallization solvent" means a solvent or combination of solvents used to crystallize a polymorph of the Compound 1 to preferentially form the desired polymorph Form I or Form II. In one embodiment, the crystallization solvent used to crystallize the polymorph Form I comprises a major portion of acetone. In another embodiment, the crystallization solvent used to crystallize the polymorph Form II comprises a major portion of methanol. The crystallization solvent may also contain one or more of the herein-described cosolvents. The cosolvent can be present in a wide range of amounts depending upon the combination solvent system being used and the polymorph being produced.

[0057] Several organic solvents can be used as cosolvents in the crystallization of Form I or Form II from acetone or methanol, respectively. The cosolvent will generally be present in amounts small enough to ensure that it does not negatively interfere with the formation of the desired polymorph. Suitable cosolvents include polar solvent, nonpolar solvent, protic solvent, aprotic solvent, acetone, methanol, ethanol, propanol, butanol, ethyl acetate, THF, DMF, diethyl ether, acetonitrile, toluene, dichloromethane, water, and combinations thereof.

[0058] The polymorph Form I can be formed by heating the polymorph Form II for a sufficient period of time and at a temperature sufficient to effect the conversion, FIG. 4 depicts a DSC thermogram of a substantially pure polymorph Form II containing approximately 92% of Form II and approximately 8% of Form I. FIG. 5 depicts a DSC thermogram of a mixture of Compound 1 containing about 46% of polymorph Form I and about 54% of polymorph Form II. These amounts have been determined by quantitating the area within the endotherm peak for each respective polymorph, summing the respective areas, and calculating the relative percent of each peak with respect to the total area. The DSC thermograms of FIGS. 4 and 5 were obtained by employing the following procedure. A sample was heated from 15° C. to 300° C., at a scan rate of 10° C. per minute, in a DSC instrument and held at 300° C. for one minute. The sample was then cooled to 15° C. by lowering the temperature at a rate of 50° C. per minute. DSC data were acquired during the temperature ramp up.

[0059] Another aliquot of the sample (Form II) of FIG. 4 was then treated in the DSC as follows to obtain the thermogram depicted in FIG. 6. The sample was heated from 15° C. to 185° C. at a scan rate of 10° C. per minute and then held at 185° C. for a period of 1 minute. After the minute, the sample was cooled to 15° C. by lowering the temperature at a rate of 50° C. per minute. After completion of this first heating cycle, the sample was heated from 15° C. to 300° C. at a scan rate of 10° C. per minute and then held at 300° C. for one minute. Finally, the sample was cooled to 15° C. by lowering the temperature at a rate of 50° C. per minute. DSC data were acquired during the second heating cycle of the DSC run. As a result of heating the sample to a temperature above the melting point of the polymorph Form II and subsequently cooling the sample, the impure polymorph Form II was converted to substantially pure polymorph Form I. Accordingly, by exposing the polymorph Form II to an elevated temperature, here 185° C. which is above the melting point of the polymorph Form II, for a sufficient period of time, here one minute, the polymorph Form II can be converted to the polymorph Form I. In a similar fashion, the mixture sample of FIG. 5 was treated as described immediately above. As a result, an impure sample of polymorph Form II containing approximately 46% of Form I and approximately 54% of Form II was converted to a substantially pure sample of the polymorph Form I (See FIG. 7).

[0060] Substantially pure Form I is also prepared by milling of Form II, or of Compound 1 that has been prepared according to known techniques. For example, milling of Form II in a fluid energy mill, jet mill, roller or ball mill, or other mechanical device to a mean particle size of approximately 1 micron to 15 microns will generally convert a portion or all of Form II to Form I. FIG. 8 is a DSC thermogram of the substantially pure polymorph Form II prior to being exposed to high energy milling and containing no detectable amounts of the polymorph Form I. By passing the polymorph Form II through a Retschmill having a 24-tooth, 1 mm screen, an impure mixture, containing significant amounts of the Form II (approximately 41%) and the Form I (about 59%), was formed, as depicted in FIG. 9. By passing the impure mixture repeatedly through a high energy mill, the polymorph Form II can be converted completely to the polymorph Form I. Likewise, an impure sample, batch or lot of the polymorph Form I containing

unacceptable amounts of the polymorph Form II is converted to substantially pure polymorph Form I by milling the impure polymorph Form I one, two, three, four, five or more times.

[0061] The above-described process can be performed in combination. Accordingly, the polymorph Form II is converted to the polymorph Form I by heating the polymorph Form I, by milling the polymorph Form II and/or by dissolving the polymorph Form II in an acetone containing solvent and crystallizing the polymorph Form I therefrom. In each case, the polymorph Form II can be pure, substantially pure or impure prior to conversion to the Form I.

[0062] The polymorph Form I is considered a heat stable form of Compound 1. By "heat stable" or "physically stable" is meant that the Form I is stable toward conversion to the polymorph Form II, although, it may be labile toward degradation to other compounds.

[0063] As the higher melting point polymorph, Form I has significant advantages over the polymorphic mixture of Compound 1 prepared according to known techniques. Specifically, Form I exhibits superior physical stability, thus allowing processing and manufacture of solid dosage forms without conversion to a different polymorphic form. This, in turn, enhances the milling and compaction properties of the drug substance.

[0064] In addition, the lower melting point polymorph, Form II, also has significant advantages over the polymorphic mixture of Compound 1 as prepared according to known techniques. Specifically, Form II exhibits superior water solubility over Form I and generally greater solubility in a range of organic solvents as compared to Form I (See Table 13). Form II is generally more soluble in polar and protic solvents than is Form I. Enhanced solubility of a compound will generally increase the bioavailability of that compound. When absorption of a drug is dissolution rate limited, use of the more soluble and faster dissolving form improves the rate and extent of bioavailability.

TABLE 13

Approximate Solubility of Form I and Form II in Various Solvents		
Solvent	Solubility (µg/mL) Form I	Solubility (µg/mL) Form II
De-ionized water	8.3	18.8
Hexane	41	50
Diethyl ether	80	51
Isopropanol	441	457
Toluene	997	645
Ethanol, absolute (100%)	1426	1722
Methanol	1740	1915
Ethyl acetate	1600	2160
Acetone	4842	6873
Acetonitrile	6246	8928
Polyethylene Glycol 400, NF	3259	10100
Tetrahydrofuran	9964	14740

[0065] For purposes of administration, a polymorph of this invention may be formulated as a pharmaceutical composition. Pharmaceutical compositions of the present invention

comprise a polymorph and a pharmaceutically acceptable carrier, wherein the polymorph is present in the composition in an amount that is effective to treat the condition of interest. Preferably, the pharmaceutical compositions of the present invention include the polymorph in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more typically from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

[0066] Pharmaceutically acceptable carriers are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain—in addition to the polymorph—diluent, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the polymorph in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed, Mack Publishing Co., Easton, Pa. 1990.

[0067] In another embodiment, the present invention provides a method for treating conditions which benefit from administration of agents which possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic, anticonvulsant, and/or skeletal muscle relaxant properties. Such condition include insomnia specifically, as well as sleep disorders generally and other neurological and psychiatric complaints, anxiety states, vigilance disorders, such as for combating behavioral disorders attributable to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, epileptic vertigo attributable to cranial trauma, and for metabolic encephalopathies.

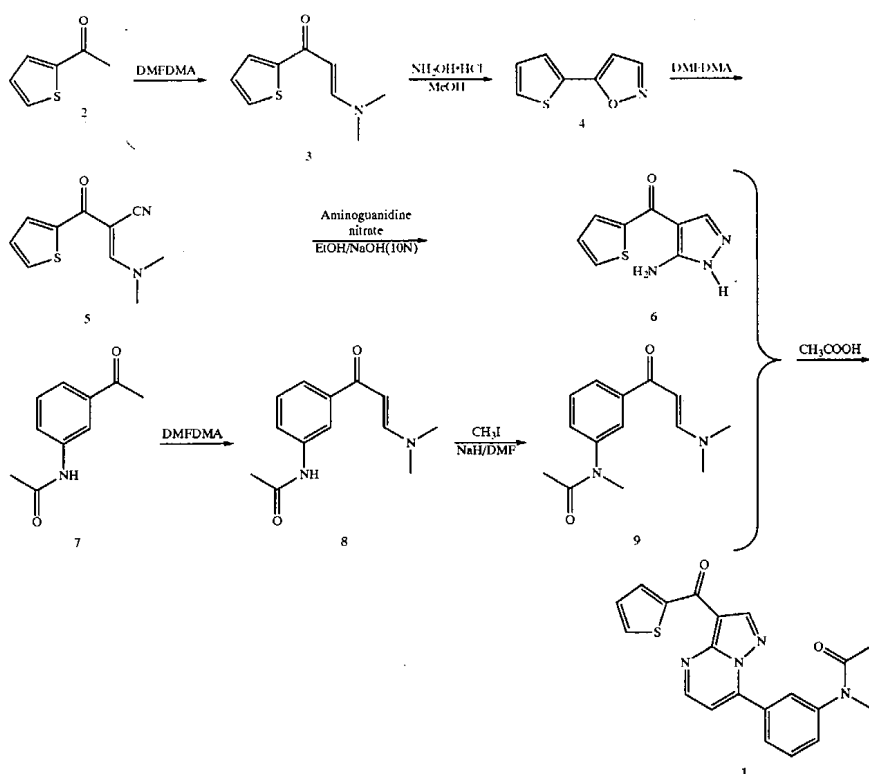
[0068] The methods of this invention include systemic administration of a polymorph as disclosed herein, preferably in the form of a pharmaceutical composition. As used herein, systemic administration encompasses both oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions that may contain buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

[0069] The following examples are offered by way of illustration, not limitation.

EXAMPLE 1

Synthesis of Compound 1

[0070] This example illustrates the synthesis of Compound 1 by know techniques, yielding Compound 1 as a mixture of polymorphic Forms I and Form II, as evidenced by the DSC thermogram of FIG. 1.



[0071] β -Dimethylamino-1-(2-thienyl)-2-propen-1-one (3)

[0072] A mixture of 2-acetylthiophene 2 (20.0 g, 159 mmol) and dimethylformamide dimethyl acetal (39 g, 327 mmol) was refluxed under nitrogen for 3 hours. The reaction mixture was cooled, concentrated to afford a dark orange solid. The solid was collected by filtration, triturated with a solution of dichloromethane and ether (1:10, 200 mL). Compound 3 was obtained as an orange solid (22.0 g, 121 mmol, 76%). GC/MS, $m/z=181$ at $tR=11.83$ min (100%). LC/MS, $[M+H]^+=182$.

[0073] 5-(2-Thienyl)isoxazole (4).

[0074] A mixture of Compound 3 (18.1 g, 100 mmol) and hydroxylamine hydrochloride (7.0 g, 101 mmol) in 100 mL of anhydrous methanol was refluxed under nitrogen for 2 hours. The reaction mixture was cooled, concentrated and partitioned between water and dichloromethane. The dichloromethane layer was dried with anhydrous sodium sulfate, filtered and concentrated to yield compound 4 as a dark yellow-orange oil (14.1 g, 93.3 mmol, 93%). GC/MS, $m/z=151$ at $tR=8.30$ min (100%). LC/MS, $[M+H]^+=152$.

[0075] α -(Dimethylamino)methylene- β -oxo-2-thiophenepropanenitrile (5)

[0076] A mixture of Compound 4 (13.0 g, 86 mmol) and dimethylformamide dimethyl acetal (22.4 g, 188 mmol) was refluxed under nitrogen for 3 hrs. Solid precipitated from the reaction mixture. The reaction mixture was cooled, diluted with dichloromethane and ether (1:10, 200 mL). The solid was collected by filtration, triturated with a solution of dichloromethane and ether (1:20, 100 mL). Compound 5 was obtained as an orange solid (13.5 g, 65.4 mmol, 76%). GC/MS, $m/z=206$ at $tR=13.39$ min (100%). LC/MS, $[M+H]^+=207$.

[0077] (3-Amino-1H-pyrazol-4-yl)-2-thienylmethanone (6)

[0078] To a mixture of aminoguanidine nitrate (17.1, 125 mmol) and 5 (20.6 g, 100 mmol) in absolute ethanol (120 mL) was added 10N NaOH. The reaction mixture was refluxed for 6 hours and the solvents were removed at reduced pressure on a rotary evaporator. Water (250 mL) was added and an initial precipitate formed and was filtered (13.3 g, 68.8 mmol, 69%). On further standing, the aqueous layer deposited an additional quantity of the desired compound 6 (3.42 g, 17.7 mmol, 18%). Compound 6 was obtained as a tan solid (total 16.72 g, 86.5 mmol, 87%). GC/MS, $m/z=193$ at $tR=13.67$ min (100%). LC/MS, $[M+H]^+=194$.

[0079] N-[3-[3-(Dimethylamino-1-oxo-2-propenyl)]-phenyl]-acetamide (8)

[0080] A mixture of 3-acetamidoacetophenone 7 (20 g, 112.9 mmol), dimethylformamide dimethyl acetal (40.3 g, 338.6 mmol) was refluxed under nitrogen for 1 hour. The reaction mixture was cooled, diluted with ethyl acetate (150 mL) and ether (150 mL). The solid was collected by filtration, triturated with a solution of ethyl acetate and hexane (1:1, 200 mL). Compound 8 was obtained as a red-orange solid (23.6 g, 101.6 mmol, 90%). GC/MS, $m/z=232$ at $tR=15.11$ min (100%). LC/MS, $[M+H]^+=233$.

[0081] N-[3-[3-(Dimethylamino)-1-oxo-2-propenyl]-phenyl]-N-methyl acetamide (9)

[0082] To a suspension of compound 8 (22.07 g, 95 mmol) in anhydrous dimethylformamide (114 mL) under nitrogen in an ice bath was added sodium hydride (4.75 g, 119 mmol, 60% in mineral oil) and, within 15 minutes, the gas evolution had ceased. To the above reaction mixture was added a solution of methyl iodide (14.2 g, 99.8 mmol). The reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction was triturated with hexane (3x150 mL) which was discarded. The reaction mixture was poured into ice water, extracted with dichloromethane (3x200 mL) which was dried with anhydrous sodium sulfate. The dry dichloromethane was concentrated to yield a solid which was triturated with a solution of ethyl acetate and hexane (1:1, 200 mL). Compound 9 was obtained as an orange solid (16.9 g, 68.6 mmol, 72%). GC/MS, $m/z=246$ at $tR=14.63$ min (100%). LC/MS, $[M+H]^+=247$.

[0083] N-Methyl-N-[3-[3-(2-thienylcarbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl]acetamide (Compound 1)

[0084] A mixture of compound 6 (11.0 g, 56.8 mmol) and compound 9 (14.0 g, 56.8 mmol) in glacial acetic acid (200 mL) was refluxed for 6 hrs. Evaporation of all volatiles on a rotary evaporator gave an oil residue, which was treated with dichloromethane (50 mL) and triturated with hexane (200 mL). The precipitate was collected by filtration and washed with 1:10 dichloromethane/hexane (100 mL). The product was dried in vacuo at 40° C. affording a mixture of Form I and Form II of Compound 1 as a pale yellow solid (16.28 g, 43.2 mmol, 76%). LC/MS, $[M+H]^+=377$. ¹H NMR (CDCl₃, 300 MHz), δ (ppm) 2.01 (s, 3H), 3.36 (s, 3H), 7.17 (d, 1H), 7.22 (dd, 1H), 7.48 (d, 1H), 7.67 (d, 1H), 7.72 (dd, 1H), 7.90-8.10 (m, 2H), 8.10 (dd, 1H), 8.73 (s, 1H), 8.85 (d, 1H).

EXAMPLE 2

Synthesis of Substantially Pure Form I

[0085] To 1.5 g of Compound 1 as prepared in Example 1 is added 100 mL of acetone. The solution is heated to reflux until the solution is homogeneous. The solution is quickly filtered through a glass-fritted funnel. The solution is allowed to gradually cool to room temperature, approximately 1 hour. The mixture is further cooled to 5° C. using an ice bath. The solid formed is collected by filtration and washed with 10 mL of cold acetone yielding 0.4 g of Form I. The mother liquor is concentrated to approximately 20 mL in vacuo. The solution is cooled to 5° C. and the solid is collected by filtration and washed with 10 mL of cold acetone affording an additional 0.5 g of Form I.

EXAMPLE 3

Synthesis of Substantially Pure Form II

[0086] To 1.4 g of Compound 1 as prepared in Example 1 is added 75 mL of methanol. The solution is heated to reflux until the solution is homogeneous. The solution is quickly filtered through a glass-fritted funnel. The solution is allowed to gradually cool to room temperature, approximately 1 hour. The mixture is further cooled to 5° C. using an ice bath. The solid formed is collected by filtration and washed with 10 mL of cold methanol yielding 0.5 g of Form II. The mother liquor is concentrated to approximately 10 mL in vacuo. The solution is cooled to 5° C. and the solid

is collected by filtration and washed with 10 mL of cold methanol affording an additional 0.4 g of Form II.

EXAMPLE 4

Crystallization of Substantially Pure Form I from an Acetone/Cosolvent Mixture

[0087] To 38 g of Compound 1, as prepared in Example 1, was added 200 mL of dichloromethane. The mixture was stirred at 25° C. until the solution was homogeneous. The solution was filtered and 150 mL of acetone was added to the filtrate. The clear, yellow solution was heated to remove the dichloromethane distillate. During distillation, an additional 200 mL of acetone was slowly added to replace the volume of the dichloromethane. Following removal of dichloromethane as evidenced by the distillate temperature, distillation was continued until the solution volume was reduced to approximately 200 mL. Heating was discontinued and the warm solution seeded with pure crystals of polymorphic Form I. The solution was gradually cooled to 5° C. and stirring was continued for several hours. The slurry was filtered and the collected crystals washed with acetone and dried in vacuo at 40° C. affording 36 g of Compound 1 as polymorphic Form I.

EXAMPLE 5

Conversion of Polymorph Form II to Form I by Milling

[0088] 5.5 g of Compound 1 consisting of approximately 100% polymorph Form II as shown in FIG. 8 was passed through a 30 mesh stainless steel screen and then through a Retsch mill with a 24 tooth rotor and a 1 mm screen. 4.0 g (approximately 73%) of Compound 1 was recovered. The recovered material was approximately 59% Form I and 41% Form II as shown in FIG. 9. This procedure could be repeated to completely convert the Form II to the Form I.

EXAMPLE 6

Conversion of Polymorph Form II to Form I by Heating

[0089] An aliquot of substantially pure polymorph Form II (having the DSC thermogram of FIG. 4) was treated in a TA 2920 Modulated Differential Scanning Calorimeter (DSC) according to the following program: Equilibrate at 15° C.

- [0090] Data storage off
- [0091] Isothermal for 1 min
- [0092] Ramp 10° C./min to 185° C.
- [0093] Isothermal for 1 min
- [0094] Ramp 50° C./min to 15° C.
- [0095] Isothermal for 1 min
- [0096] Data storage on
- [0097] Ramp 10° C./min to 300° C.
- [0098] Isothermal for 1 min
- [0099] Data storage off
- [0100] Ramp 50° C./min to 15° C.

[0101] The resulting thermogram (FIG. 6) showed substantially pure polymorph Form I (as evidenced by the endotherm at 193.77).

[0102] An aliquot of Compound 1 consisting of a mixture of Form I and Form II as shown in FIG. 5 was treated in the same manner, giving the thermogram of FIG. 7 which shows only Form I (endotherm at 195.78 only).

[0103] The above is a detailed description of particular embodiments of the invention. It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

We claim:

- 1. A substantially pure polymorph Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide exhibiting a predominant endotherm at about 192-198° C. as measured by Differential Scanning Calorimeter.
- 2. The substantially pure polymorph Form I of claim 1, wherein said polymorph Form I comprises less than about 6% by weight of a polymorph Form II.
- 3. The substantially pure polymorph Form I of claim 2, wherein said polymorph Form I comprises less than about 2% by weight impurities, less than about 1% by weight water, and less than about 0.5% by weight residual organic solvent.
- 4. The substantially pure polymorph Form I of claim 2, wherein said polymorph exhibits a predominant endotherm at about 195-197° C.
- 5. The substantially pure polymorph Form I of claim 2, wherein said polymorph has about 2 molecules per cell and is of the P1bar space group as determined by single-crystal X-ray crystallography.
- 6. The substantially pure polymorph Form I of claim 2, wherein said polymorph has crystal dimensions of about 0.12 mmx0.05 mmx0.015 mm and a volume of about 913, as determined by single-crystal X-ray crystallography.
- 7. The substantially pure polymorph Form I of claim 2, wherein said polymorph has a calculated density of about 1.37, as determined by single-crystal X-ray crystallography.
- 8. The substantially pure polymorph Form I of claim 2, further characterized by the following single-crystal X-ray crystallography bond distances:

A	B	Distance
S(1)	C(2)	1.728(9)
S(1)	C(5)	1.763(7)
O(7)	C(6)	1.263(8)
O(26)	C 25	1.306(12)
N(10)	N(11)	1.392(7)
N(10)	C(9)	1.352(8)
N(11)	C(12)	1.404(7)
N(11)	C(16)	1.415(8)
N(15)	C(14)	1.343(8)
N(15)	C(16)	1.357(9)
N(23)	C(19)	1.514(10)
N(23)	C(24)	1.530(10)

-continued		
A	B	Distance
N(23)	C(25)	1.234(9)
C(2)	C(3)	1.365(10)
C(3)	C(4)	1.434(9)
C(4)	C(5)	1.400(10)
C(5)	C(6)	1.490(10)
C(6)	C(8)	1.483(9)
C(8)	C(9)	1.418(9)
C(8)	C(16)	1.421(9)
C(12)	C(13)	1.380(9)
C(12)	C(17)	1.486(9)
C(13)	C(14)	1.428(9)
C(17)	C(18)	1.415(10)
C(17)	C(22)	1.424(8)
C(18)	C(19)	1.387(10)
C(19)	C(20)	1.409(9)
C(20)	C(21)	1.404(10)
C(21)	C(22)	1.412(9)
C(25)	C(27)	1.584(13)
C(2)	H(1)	.921(7)
C(3)	H(2)	.978(8)
C(4)	H(3)	.945(7)
C(9)	H(4)	.954(7)
C(13)	H(5)	.949(6)
C(14)	H(6)	.961(7)
C(18)	H(7)	.940(6)
C(20)	H(8)	.958(7)
C(21)	H(9)	.952(6)
C(22)	H(10)	.950(7)
C(24)	H(11)	.943(8)
C(24)	H(12)	.939(7)
C(24)	H(13)	.954(7)
C(27)	H(14)	.953(8)
C(27)	H(15)	.942(7)
C(27)	H(16)	.937(8)

9. A substantially pure polymorph Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide exhibiting a predominant endotherm at about 172-179° C. as measured by a Differential Scanning Calorimeter
10. The substantially pure polymorph Form II of claim 9, wherein said polymorph Form II comprises less than about 20% by weight of a polymorph Form I.
11. The substantially pure polymorph Form II of claim 10, wherein said polymorph Form II comprises less than about 2% by weight impurities, less than about 1% by weight water, and less than about 0.5% by weight residual organic solvent.
12. The substantially pure polymorph Form II of claim 10, wherein said polymorph exhibits a predominant endotherm at about 173-177° C.
13. The substantially pure polymorph Form II of claim 10, wherein said polymorph has about 4 molecules per cell and is of the P2₁/a space group, as determined by single-crystal X-ray crystallography.
14. The substantially pure polymorph Form II of claim 10, wherein said polymorph has crystal dimensions of about 0.35 mm×0.20 mm×0.12 mm and a volume of about 1797, as determined by single-crystal X-ray crystallography.
15. The substantially pure polymorph Form II of claim 10, wherein said polymorph has a calculated density of about 1.39, as determined by single-crystal X-ray crystallography.
16. The substantially pure polymorph Form II of claim 10, further characterized by the following single-crystal X-ray crystallography bond distances:

A	B	Distance
S(1)	C(2)	1.703(8)
S(1)	C(5)	1.734(6)
O(7)	C(6)	1.233(7)
O(26)	C(25)	1.267(9)
N(10)	N(11)	1.373(6)
N(10)	C(9)	1.332(7)
N(11)	C(12)	1.391(7)
N(11)	C(16)	1.389(7)
N(15)	C(14)	1.328(7)
N(15)	C(16)	1.336(8)
N(23)	C(19)	1.451(9)
N(23)	C(24)	1.486(8)
N(23)	C(25)	1.295(9)
C(2)	C(3)	1.366(9)
C(3)	C(4)	1.405(9)
C(4)	C(5)	1.377(9)
C(5)	C(6)	1.453(9)
C(6)	C(8)	1.480(8)
C(8)	C(9)	1.379(8)
C(8)	C(16)	1.410(8)
C(12)	C(13)	1.353(8)
C(12)	C(17)	1.484(8)
C(13)	C(14)	1.405(8)
C(17)	C(18)	1.392(8)
C(17)	C(22)	1.379(9)
C(18)	C(19)	1.406(9)
C(19)	C(20)	1.369(9)
C(20)	C(21)	1.379(9)
C(21)	C(22)	1.379(8)
C(25)	C(27)	1.548(10)
C(2)	H(1)	.950(7)
C(3)	H(2)	.950(7)
C(4)	H(3)	.949(6)
C(9)	H(4)	.950(6)
C(13)	H(5)	.950(6)
C(14)	H(6)	.950(6)
C(18)	H(7)	.950(7)
C(20)	H(8)	.950(6)
C(21)	H(9)	.950(7)
C(22)	H(10)	.949(7)
C(24)	H(11)	.952(8)
C(24)	H(12)	.949(8)
C(24)	H(13)	.948(8)
C(27)	H(14)	.952(8)
C(27)	H(15)	.949(8)
C(27)	H(16)	.952(7)

17. A process for preparing substantially pure Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide, comprising the steps of:
- forming a solution of a crystallization solvent comprising acetone and N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide; and
- cooling the solution to form a mass of crystals, and collecting the crystals to the Form I.
18. The process of claim 17 further comprising the step of: drying the collected crystals to yield substantially pure Form I.
19. The process of claim 17, wherein the step of forming a solution comprises the steps of:
- providing N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)-acetamide; and
- contacting the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)-acetamide with a crystallization solvent.

20. The process of claim 19, wherein the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide is provided as a solid.

21. The process of claim 19, wherein the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide is provided as a concentrate in an organic cosolvent.

22. The process of claim 21, wherein the cosolvent comprises methylene chloride.

23. The process of claim 19 further comprising the step of: heating the crystallization solvent to effect dissolution of the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide.

24. A polymorph Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide made according to the process of any one of claims 17-23.

25. A process for preparing substantially pure Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide comprising the steps of:

forming a solution of a crystallization solvent comprising methanol and N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide; and

cooling the solution to form a mass of crystals, and collecting the crystals to the Form II.

26. The process of claim 25 further comprising the step of: drying the collected crystals to yield substantially pure Form II.

27. The process of claim 25, wherein the step of forming a solution comprises the steps of:

providing N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)-acetamide; and

contacting the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)-acetamide with a crystallization solvent.

28. The process of claim 27, wherein the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide is provided as a solid.

29. The process of claim 27, wherein the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide is provided as a concentrate in an organic cosolvent.

30. The process of claim 29, wherein the cosolvent comprises methylene chloride.

31. The process of claim 27 further comprising the step of:

heating the crystallization solvent to effect dissolution of the N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide.

32. A process for converting a polymorph Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide to a polymorph Form I, the process comprising the steps of:

providing a composition comprising the polymorph Form II according to claim 9;

heating the composition to a temperature higher than the melting point of the polymorph Form II; and p1 cooling the composition to form the polymorph Form I according to claim 1.

33. A polymorph Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide made according to the process of claim 32.

34. A process for converting a polymorph Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide to a polymorph Form I, the process comprising the steps of:

providing a composition comprising the polymorph Form II according to claim 9; and

milling the composition one or more times to form the polymorph Form I according to claim 1.

35. A polymorph Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide made according to the process of claim 34.

36. A process for converting a polymorph Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide to a polymorph Form I, the process comprising the steps of:

providing a composition comprising the polymorph Form II according to claim 9;

heating the composition at a temperature above ambient temperature but below the melting point of the polymorph Form II for a period of time sufficient to convert the polymorph Form II to the polymorph Form I according to claim 1; and

cooling the polymorph Form I.

37. A polymorph Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[5- α]-pyrimidin-7-yl}phenyl)acetamide made according to the process of claim 36.

38. A composition comprising substantially pure Form I of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide according to claim 2 and a pharmaceutically acceptable carrier.

39. The composition of claim 38, wherein the composition is formulated for oral administration.

40. The composition of claim 39, wherein the composition is in the form of a pill, capsule or tablet.

41. The composition of claim 40, wherein the Form I is present in a unit dosage form at an amount of about 0.1 to 250 mg.

42. A composition comprising substantially pure Form II of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- α]-pyrimidin-7-yl}phenyl)acetamide according to claim 10 and a pharmaceutically acceptable carrier.

43. The composition of claim 42, wherein the composition is formulated for oral administration.

44. The composition of claim 43, wherein the composition is in the form of a pill, capsule or tablet.

45. The composition of claim 44, wherein the Form II is present in a unit dosage form at an amount of about 0.1 to 250 mg.

46. A method for treating insomnia in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form I of claim 1.

47. A method for inducing sleep in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form I of claim 1.

48. A method for inducing sedation or hypnosis in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form I of claim 1.

49. A method for inducing skeletal muscle relaxation in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form I of claim 1.

50. A method for treating insomnia in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form II of claim 9.

51. A method for inducing sleep in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form II of claim 9.

52. A method for inducing sedation or hypnosis in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form II of claim 9.

53. A method for inducing skeletal muscle relaxation in a patient in need thereof, comprising administering to the patient an effective amount of substantially pure Form II of claim 9.

* * * * *

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

PATENTE DE INVENCION

MODELO DE UTILIDAD

USUARIO RADICADOR

- Indicación de que se solicita la concesión de una patente.
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.
- Descripción de la invención.
- Dibujos de ser estos pertinentes.
- Comprobante de Pago de las tasas establecidas.

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DISEÑO INDUSTRIAL ()

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

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ESQUEMA DE TRAZADO ()

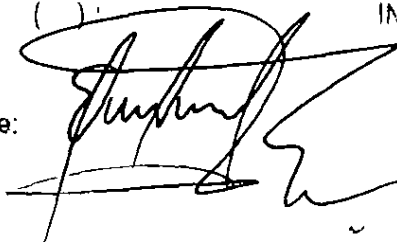
- Indicación de que solicita el registro de un Esquema de trazado
- Datos de identificación del solicitante o de la persona que presenta La solicitud.
- Representación gráfica del esquema de trazado
- Comprobante de pago de las tasas establecidas.

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Firma Responsable:



Fecha:

SUPERINDUSTRIA Y COMERCIO

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Folios: 69

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



Industria y Comercio
SUPERINTENDENCIA

Folio 71

2020
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Doctor(a)
DILIA RODRIGUEZ D'ALEMAN

Oficio N° 12296

ASUNTO:	Radicación N°	05-9445
	Solicitud internacional	PCT/US2003/026870
	Fecha inicio fase nacional	26/03/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- 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.
- 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 486/00.

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

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

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

Carrera 13 No. 27-00 Pisos 5, 7 y 10

El anterior requerimiento fue notificado por fijación en lista de
fecha, 04 MAR. 2005

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