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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-097869- -00013-0000

Fecha: 2011-03-02 16:52:20 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 412 REPOSPRESRECU Folios: 46

Señor Superintendente

SUPERINTENDENCIA DE INDUSTRIA Y

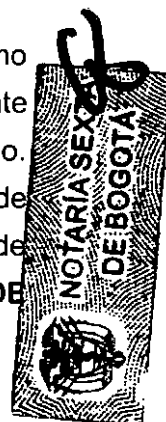
E. S. D.

Trámite : 011
Evento : 379
Actuación : 412

Referencia : Expediente No. 05.097.869
Asunto : Solicitud de Patente para:
"MÉTODO PARA PREPARAR SALES DE ADICIÓN DE ÁCIDOS
DE COMPUESTOS POLIÁCIDOS BÁSICOS"
Solicitante : KOWA CO., LTD.
Clase : A61K 031/496, A61P 001/000, A61P 003/006, A61P 009/000, A61P
009/010, A61P 013/012, A61P 035/000, A61P 043/000, C07D
401/012, C07D 417/012
Fecha de Solicitud : Septiembre 27 de 2005

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, abogada con Tarjeta Profesional No. 23.555, obrando como apoderada de **KOWA CO., LTD.**, solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **No. 03996** de fecha 31 de enero de 2011, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para "**MÉTODO PARA PREPARAR SALES DE ADICIÓN DE ÁCIDOS DE COMPUESTOS POLIÁCIDOS BÁSICOS**" a favor de **KOWA CO., LTD.**



II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución **No. 03996** de fecha 31 de enero de 2011, fue notificada mediante edicto No. **2035** desfijado el veintitrés (23) de febrero de dos mil once (2011), por lo que el término

para interponer el recurso de reposición vence el dos (02) de marzo de dos mil once (2010). En consecuencia, me encuentro dentro de la oportunidad legal.

III. FUNDAMENTO DE LA RESOLUCIÓN N. 03996

Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:

3.1 Negar el privilegio de patente para la invención "MÉTODO PARA PREPARAR SALES DE ADICIÓN DE ÁCIDOS DE COMPUESTOS POLIÁCIDOS BÁSICOS".

3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:

"El estado de la técnica más cercano es D1, toda vez que divulga un proceso de preparación de las sales de adición del compuesto de fórmula (I), las cuales también pueden ser preparadas como solvato(s) con un solvente para la reacción o para la recristalización especialmente como hidrato (Fl. 227, Pág. 18, líneas 35-40, resumen)."

"El método reivindicado por la presente solicitud se diferencia del procedimiento divulgado en D1, en que enseña el empleo de clorhidrato de piridina (hidrocloruro de piridina), como fuente del anión alterna para obtener las sales adición, en vez de los métodos comunes conocidos en el estado de la técnica..."

"El hecho de incluir una fuente de anión diferente a la divulgada en D1, causa que por medio del método de preparación se obtengan sales de adición alternas de un compuesto poliacídico básico o un aducto de agua que tiene un sitio(s) básico más fuerte que la piridina."

"Por su parte, la anterioridad D2 describe una manera de solucionar el problema técnico objetivo de la solicitud, que consiste en *"proveer un método de preparación de una sal de adición de un compuesto poliacídico básico o un aducto de agua que tiene más de un sitio básico más fuerte que la piridina"*, mediante un método de producción de clorhidrato de paroxetina, utilizando una fuente de cloruro de hidrógeno sólida, conveniente, barata y suave, sin el empleo de instalaciones de manejo de gases tóxicos bajo condiciones leves, tratado con el clorhidrato de una amina, donde, por ejemplo, se puede usar clorhidrato de piridina y así se evita la formación de impurezas causadas por el uso de ácidos minerales fuertes para la formación de sales (ver resumen de D2)."



“En consecuencia, el método reivindicado carece de nivel inventivo, ya que se deriva de manera evidente del estado del arte y resulta obvio para una persona normalmente versada en la materia técnica y, por ende, no cumple con lo dispuesto en el artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.”

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

- 4.1. Revocar la Resolución No. **No. 03996** de fecha 31 de enero de 2011.
- 4.2. Conceder el privilegio de patente de invención para **“MÉTODO PARA PREPARAR SALES DE ADICIÓN DE ÁCIDOS DE COMPUESTOS POLIÁCIDOS BÁSICOS** a favor de **KOWA CO., LTD.**

V. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, ya que la presente solicitud posee nivel inventivo a la luz de los documentos EP 0 987 254 (D1) y WO 00/32593 (D2).

La anterior afirmación tiene justificación jurídica y técnica por las siguientes razones:

- 5.1. **Violación del artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina:**

De acuerdo con el artículo 18 de la Decisión 486:

“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”



Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe

colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aportan un salto tecnológico en la regla técnica.

A este respecto manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

Inicialmente, queremos poner de presente que la presente solicitud comprende dos invenciones íntimamente ligadas pero diferentes, relacionadas con un método (reivindicaciones 1-2) y un producto (reivindicaciones 3-4).

Por lo tanto, no resulta aceptable la conclusión del Despacho cuando afirma que las reivindicaciones 2-4 son dependientes de la reivindicación 1. En efecto, las reivindicaciones 3-4 no solamente no son dependientes de la 1 sino que comportan una invención diferente, sobre la cual se debe adelantar un examen de patentabilidad independiente.

Teniendo en cuenta lo anterior, respetuosamente solicitamos al Despacho proceder de esta manera, esto es, evaluando por separado la patentabilidad de cada uno de los dos grupos de invenciones presentes en la solicitud y, llegado el caso, hacer uso de la facultad que le otorga la legislación actual de otorgar parcialmente la patente solicitada para las invenciones que cumplan los requisitos de patentabilidad.

Así entonces, deseamos poner de presente que aunque ciertas sales de clorhidrato de los compuestos reclamados se encuentran descritos en la anterioridad D1 (EP0987254), como lo es el Diclorohidrato de 2-[4-[2-(Bencimidazol-2-tioil)etil]piperazin-1-il]-N-(2,4-bis (tiometil)-



6-metil-3-piridil) acetamida, cuyo método de preparación es descrito en el ejemplo 37 de dicho documento, el compuesto específico Monoclorhidrato de 2-[4-[2-(Bencimidazol-2-tioil)etil]piperazin-1-il]-N-(2,4-bis(tiometil)-6-metil-3-piridil) acetamida, reclamado en el pliego reivindicatorio de la presente solicitud no es mencionado en dicha anterioridad.

Sin embargo, como se menciona en el último párrafo de la página 2 de las especificaciones de la presente solicitud, los compuesto de 2-[4-[2-(Bencimidazol-2-tioil)etil]piperazin-1-il]-N-(2,4-bis(tiometil)-6-metil-3-piridil) acetamida son reconocidos derivados de la piperacina que puede presentar una actividad inhibidora de ACAT, pero presentan la limitación en cuanto a que al ser cristalizados en su forma de base libre, su absorción oral no es satisfactoria dado que los cristales formados no son uniformes y su estabilidad física y solubilidad en agua suelen ser relativamente bajas. Este es el caso del Diclorohidrato de 2-[4-[2-(Bencimidazol-2-tioil)etil]piperazin-1-il]-N-(2,4-bis(tiometil)-6-metil-3-piridil) acetamida, descrito en el documento D1, el cual presenta los problemas típicos en cuestión de cristalización, estabilidad térmica y propiedades higroscópicas, entre otros, lo cual a su vez se refleja en la obtención diferentes productos no apropiados como agentes farmacéuticos.

Como es ampliamente conocido en el desarrollo de nuevos fármacos, parte de las funciones del preformulador farmacéutico corresponde el seleccionar y proporcionar la forma de la sal en estado cristalino más apropiada, de forma tal que su actividad farmacológica estudiada sea observada una vez suministrada al paciente. Para el caso del derivado de la piperidina y de acuerdo a los datos de la Tabla 1 de las especificaciones de la solicitud bajo estudio, resulta evidente que las mejores propiedades se logran para la sal monoclorhidrato de dicho derivado. Dicha sal se caracteriza por tener una alta cristalinidad, no presenta higroscopicidad, muestra una máxima estabilidad térmica sin cambios significativos de peso por condiciones tales que conlleven a la deshidratación o deshidrocloridación; no presenta polimorfismo y no es afectada por la presencia de residuos de ácido clorhídrico. Por lo tanto, resulta evidente que la sal monoclorhidrato es una sal de adición de ácido preferente y es útil como ingrediente farmacéutico con respecto a otras sales de adición de ácido obtenidas por medio de métodos diferentes para la inhibición de ACAT y uso en tratamiento y profilaxis como aplicación industrial.



El método reivindicado en la presente solicitud y por el cual se obtiene la sal monoclorhidrato del derivado de la piperidina se diferencia del método reclamado en el documento D1, toda vez que este parte del principio de ajustar el número de moles de ácido agregado en el derivado de piperidina, con el fin de fijar los sitios básicos a los cuales

se adhiere el ácido y reproducir específicamente dicha sal de adición con mejores propiedades (sal monoclórhidrato), minimizando la producción de otras sales de clórhidrato, como lo son las sales de tetra-, tri-, y diclorhidrato.

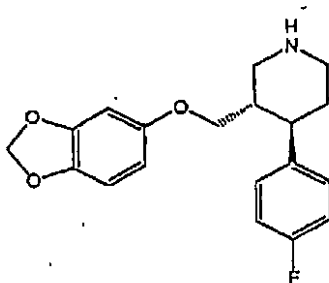
De acuerdo a lo anterior, no es correcto afirmar que al divulgar una sal diclorhidrato del compuesto de la actual solicitud, el documento D1 sirve de evidencia que la sal se forma exitosamente y que existe la posibilidad tangible que se forme la sal monoclórhidrato mediante los métodos conocidos por una persona del oficio normalmente versada en la materia.

A este respecto, se debe tener en cuenta la declaración realizada por Kimiyuki Shibuya, Ph. D. ante la Oficina de Patentes de Estados Unidos en la cual analiza las pruebas comparativas entre las sales mono- y diclorhidrato del derivado de piperidina. De dicha declaración se puede concluir que la sal diclorhidrato del documento D1 no presenta una cristalización significativa, como se evidencia por los picos del espectro de difracción por rayos X para dicha sal en especial. Lo que es más, la sal diclorhidrato es altamente inestable como se concluye a partir de la pérdida de agua y HCL y su consecuente reducción gradual de masa con el aumento de temperatura en el espectro TG-DSC. Así mismo, y probablemente más importante aun resulta el hecho que la tarea de determinar una dosis uniforme del componente activo se ve ampliamente comprometida en vista de la posible descomposición ocasionada por la inestabilidad de la sal diclorhidrato.

De esta forma, resulta claro que una persona versada en la materia no se vería motivada por las enseñanzas del documento citado D1, en cuanto dicho documento ni señala ni sugiere la sal monoclórhidrato o su método de obtención, la cual provee como ventaja adicional a lo revelado en la presente solicitud que dicha sal presenta una alta cristalinidad uniforme y estabilidad, y permanencia de su masa al no ser propenso a su desintegración bajo condiciones ambientales variadas; y por consiguiente, puede ser usada como agente farmacológico para el tratamiento de diferentes enfermedades, a diferencia de la sal diclorhidrato reclamada en el documento D1.

Adicional a lo anterior, resulta necesario poner de presente que el clórhidrato de paroxetina de acuerdo al documento D2, solo presenta un sitio básico, como se observa en la siguiente estructura química:



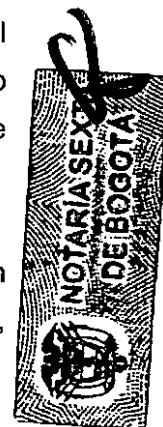


Por lo tanto, contrario a las consideraciones del Examinador, una persona versada en la materia no tendría ningún incentivo a considerar dicho documento al estar enfrentado al problema que se presenta en la solicitud partiendo del hidrocloreuro de piridina, ya que aunque cercano estructuralmente al anillo de piperazina, el hecho de presentar un solo sitio básico carbocíclico con nitrógeno, no da indicio alguno de cómo ajustar el número de moles de ácido agregado en el derivado de piperidina y fijar los sitios básicos dentro de los a los cuales se adhiere el ácido entre 4 sitios básicos, correspondientes a un átomo de nitrógeno básico en el anillo imidazol, dos átomos de nitrógeno en el anillo de piperazina y un átomo de nitrógeno del anillo piridina, para la obtención específica de la sal de adición de monoclórhidrato, sin producir cantidades significativas de las otras sales de adición tetraclorehidrato, triclorehidrato, y diclorehidrato, cuyas propiedades no son apropiadas o deseadas para su uso dentro de una formulación farmacológica.

Así las cosas, la sal de la presente invención resuelve de manera sorprendente e inesperada el problema técnico propuesto en la presente solicitud, motivo por el cual no se puede considerar que una persona versada en la materia derivaría de manera obvia el artículo reivindicado al tomar como referencia las enseñanzas de las anterioridades debido a la sal diclorohidrato de la anterioridad EP 0 987 254 (D1) y del uso del hidrocloreuro de piridina con un único sitio básico de la anterioridad WO 00/32593 (D2).

En consecuencia, de esta manera se desvirtúa lo manifestado por su Despacho con respecto a que la presente invención no había superado un prejuicio técnico y por ende, queda acreditado el nivel inventivo de la misma.

Por último, queremos poner de presente que aunque nos encontramos de acuerdo con la soberanía y autonomía de su Oficina para realizar el examen de patentabilidad de las solicitudes de patentes, consideramos relevantes tener de presente que la solicitud bajo estudio ha sido otorgada tanto en Europa como en Estados Unidos. Atentamente



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solicitamos reconsiderar la negativa en vista de los pliegos concedidos en Europa como en Estados Unidos, así como las respuestas a las acciones oficiales y declaraciones realizadas, anexas a este recurso.

VI. PETICIONES

Ruego a Usted entonces, lo siguiente:

- 6.1. Que se revoque el artículo PRIMERO de la Resolución No. 03996 en cuanto niega el privilegio de patente para el capítulo reivindicatorio de la presente invención.
- 6.2. Que se otorgue, total o parcialmente, la respectiva patente de invención de acuerdo con el último pliego reivindicatorio sometido a su consideración.

VII. NOMBRE Y DIRECCIÓN DEL RECURRENTE

El nombre y la dirección del recurrente son:

KOWA CO., LTD.

6-29, Nishiki 3-chome, naka-Ku

Nagoya-shi, Aichi 460-8625

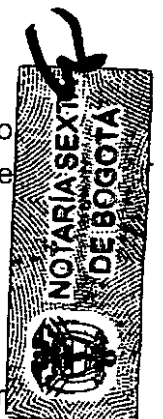
Japón

VIII. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaria de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4º, de esta ciudad de Bogotá, D.C.

IX. ANEXOS

- 9.1. Declaración presentada ante la Oficina de Patentes de Estados Unidos por el Dr. Kimiyuki Shibuya.
- 9.2. Respuestas a las acciones oficiales correspondientes a la Solicitud Europea No. 04 715 495.0 tal como se presentaron en Junio 6 de 2008 y Noviembre 25 de 2009.



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- 9.3. Pliego reivindicatorio otorgado por la Oficina Europea de Patentes y que fue modificado junto con la respuesta presentada en Noviembre 25 de 2009.
- 9.4. Pliego reivindicatorio otorgado por la Oficina de Patentes de Estados Unidos correspondiente a la patente No. 7 750 150.

Señor Superintendente,

Luiz Clemencia de Páez
LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-14890-841-001-9
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No. M-2011-188169\LLG



9

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C.

Ante mí AMPARO QUINTERO ARTURO,

02 MAR 2011

NOTARIA SEXTA DEL CÍRCULO DE

BOGOTÁ, D.C.

Comercio (erón)

[Handwritten signature]
[Handwritten signature]

Quien(es) exhibió(eron) la(s) C.C.

34716349
882355

Y declaró(aron) que la(s) firma(s) que se hacen en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

Lea Clemencia Gómez

TPA 23555 CST



Docket No.: 276446US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

GROUP: 1624

Kimiyuki SHIBUYA, et al.

SERIAL NO: 10/545,200

EXAMINER: JARRELL, N.

FILED: August 11, 2005

FOR: PROCESS FOR PRODUCING ACID ADDUCT SALT OF POLYACIDIC
BASE COMPOUND

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes Kimiyuki Shibuya who deposes and states:

1. That I am a graduate of Tohoku University and received a BS degree in 1979, an MS degree in 1981 and a Ph. D. degree in 1994.
2. That I have been employed by KOWA COMPANY, LTD., for 28 years as a researcher in the field of Medicinal and Organic Chemistry.
3. That I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.
4. That the following experiments were carried out by me or under my direct supervision and control.
5. The compound of Example 1 in the present specification which is a monohydrochloride of formula (1) was compared to the tetrahydrochloride and dihydrochloride of Shibuya, Example 32.
6. The base compound of formula (1) corresponding to that in Example 1 on page 21 of the specification is:

2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide.

7. Table A: Comparison of physical properties of the monohydrochloride of the invention with the same compound as tetrahydrochloride, dihydrochloride or as a base compound.

Example 1

Salt	Monohydrochloride 0.9-water adduct (invention)	Tetrahydrochloride 2-water adduct	Dihydrochloride Ex 32 of P1	Base compound
Melting point (°C)	194-196	193-196	214-218	92-95
Powder X-ray	Crystallinity	Low crystallinity	Non crystallinity	Low crystallinity
TG	No change until decomposition	Gradual removal of water and HCl	Gradual removal of water and HCl	No change
DSC/DTA	1 peak at 194°C	1 peak at 188°C	Non peak	1 peak at 104.5°C

8. As summarized above, the monohydrochloride of the invention is crystalline (see monohydrochloride powder X-ray diffraction pattern below), exhibits no change until decomposition (see monohydrochloride TG-DSC measurements below).

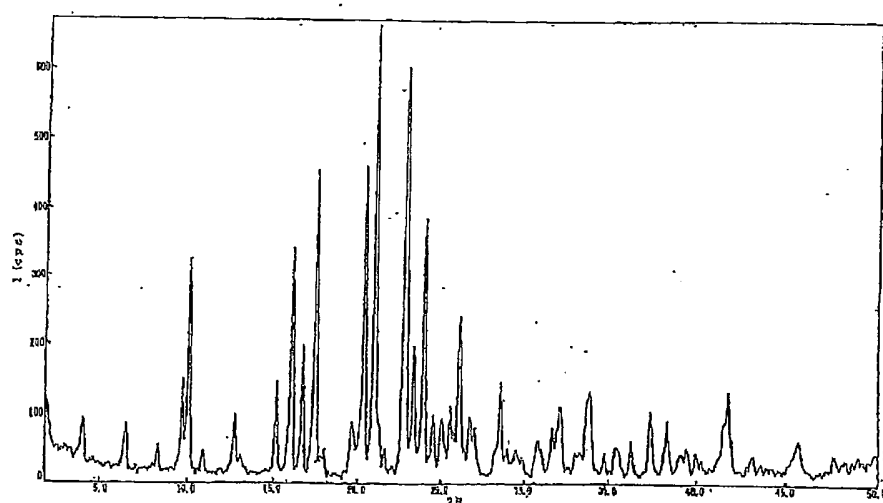
The dihydrochloride salt, which corresponds to the compound of Shibuya, has extremely low or no crystallinity (see dihydrochloride powder X-ray diffraction pattern below which lacks sharp peaks). Moreover, the dihydrochloride salt exhibits instability, because water and HCl are gradually removed (see dihydrochloride TG-DSC measurements which show gradual reduction of mass due to loss of water and HCl with increasing temperature).

The tetrahydrochloride salt and the base compound both exhibit low crystallinity as apparent from their respective powder X-ray diffraction patterns. The tetrahydrochloride salt is unstable based on TG-DSC analysis, undergoing gradual removal of water and HCl with increasing temperature.

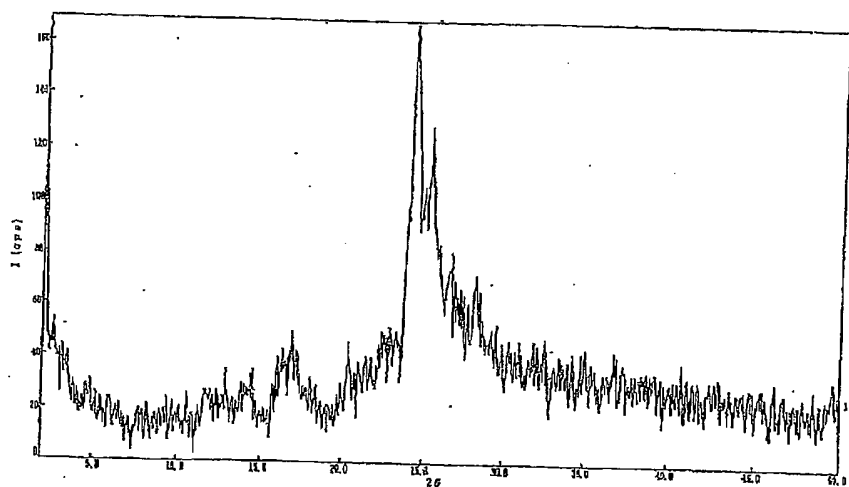
As evident from Table A, only the monohydrochloride salt of the invention exhibits a high degree of crystallinity and has high stability as determined by TG-DSC measurements.

9. The raw data summarized in Table A are provided below.

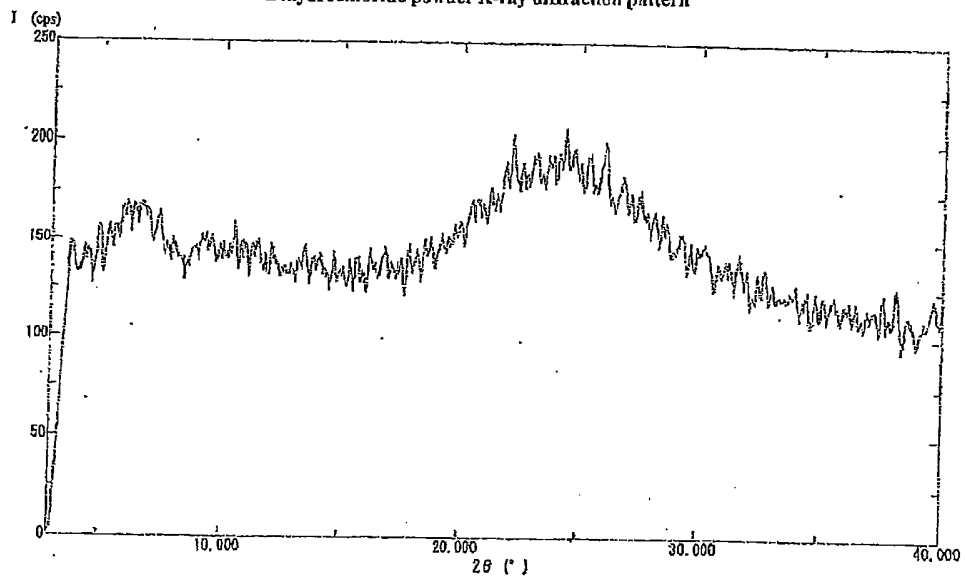
Monohydrochloride powder X-ray diffraction pattern

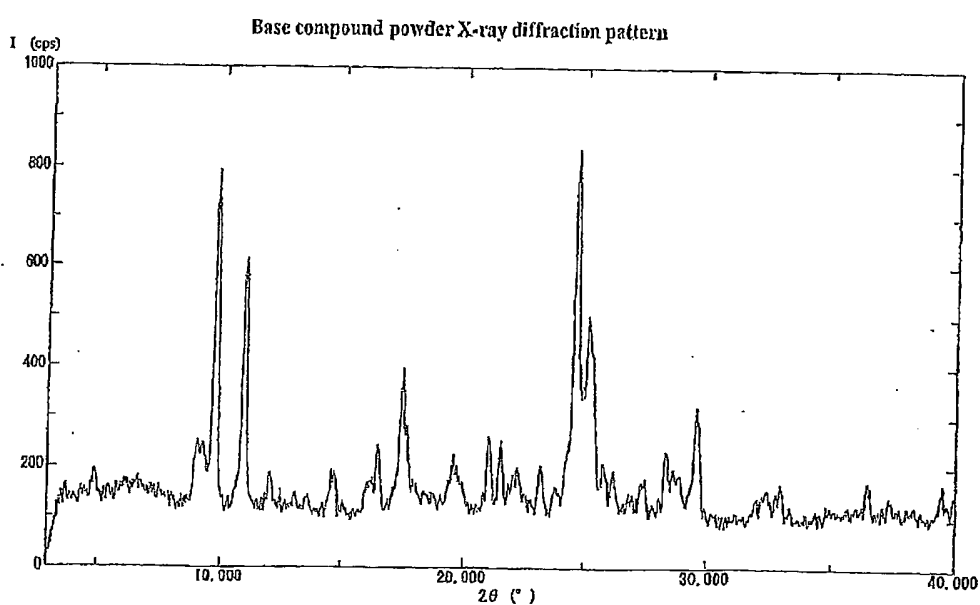


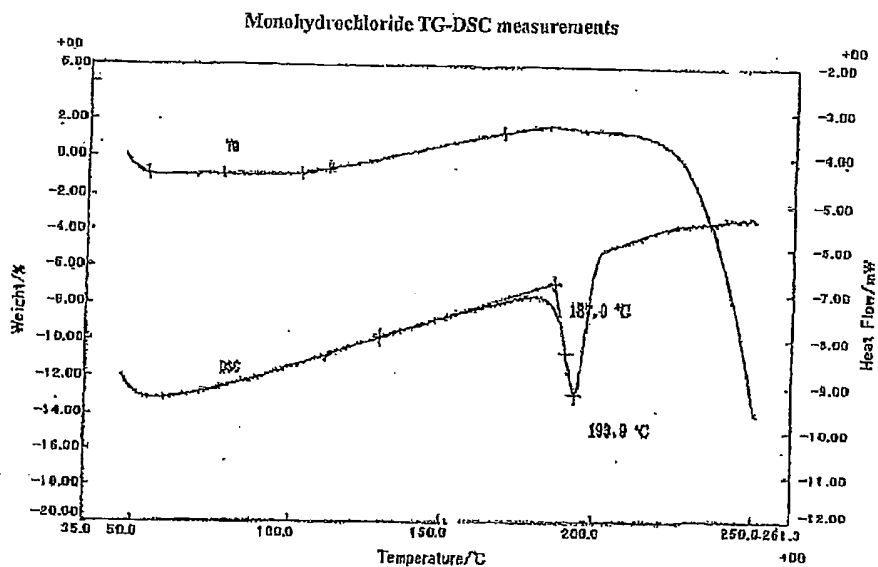
Tetrahydrochloride powder X-ray diffraction pattern

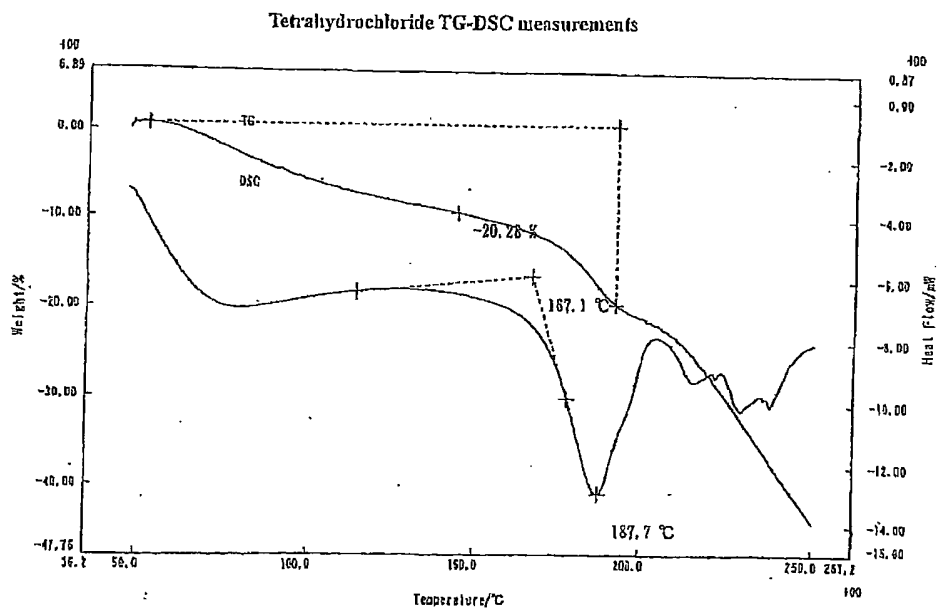


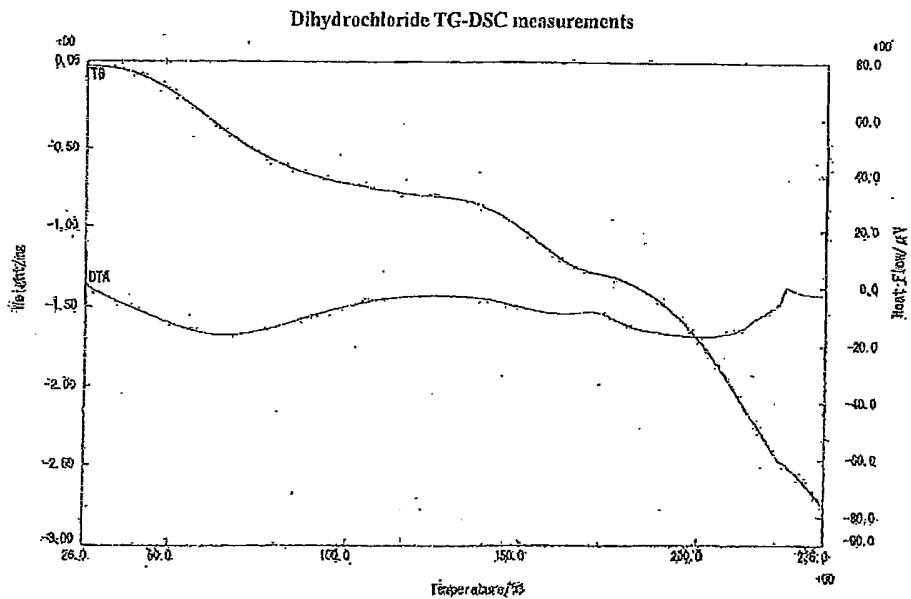
Dihydrochloride powder X-ray diffraction pattern

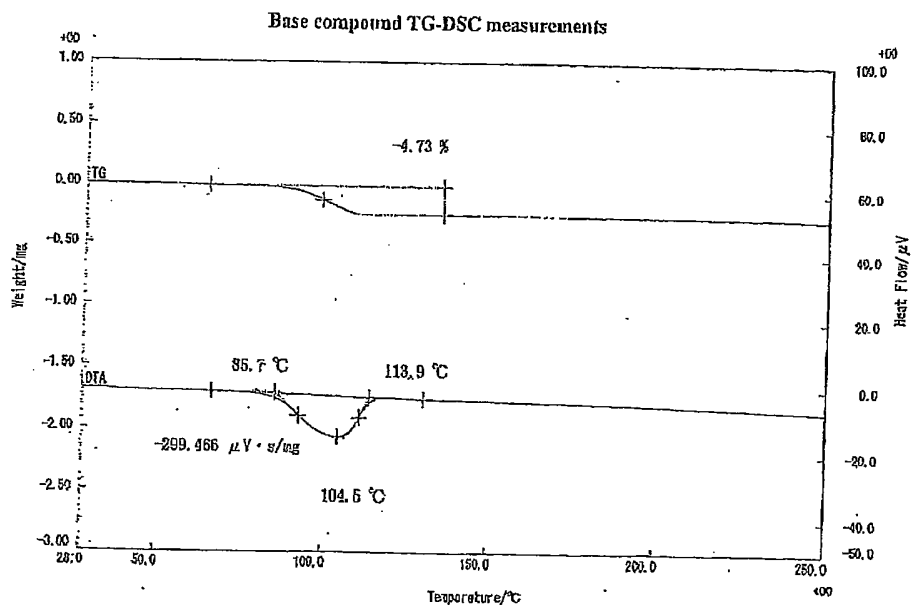












10. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

11. Further deponent saith not.

Customer Number

22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 05/06)

Signature

Date

H. Siskaya

March 10, 2009

WÄCHTERSCHÄUSER & HARTZ

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Prof. Dr. Günter Wächtershäuser (-2008)
Dr. (USA) Nikolai F. Hartz
Dr. sc. nat. Wolfgang Blodig

Consultant:
Prof. Dr. Günter Wächtershäuser

EUROPEAN PATENT OFFICE
Erhardtstraße 27
80469 München

June 06, 2008

Re: European Patent Application
No.: 04 715 495.0
Kowa Company, Ltd.
Our Ref.: EA-PCT-13415

*Response to OA (Corresponding EP Application
04 715 495.0.)*

Response to the Communication dated November 28, 2007

A new set of claims 1 to 12 is filed. For disclosure purposes, reference is made to page 4, lines 20 to 22 of the application as filed.

The following references are filed in support of inventive activity of the present invention:

- Reference 1: Handbook of Pharmaceutical Salts: Properties, Selection, and Use by P. Heinrich Stahl, C.G. Wermuth, Wiley-VCH (Helvetica Chimica Acta), 135-160, 2002
- Reference 2: Pharmaceutical Research, Vol. 18, No. 6, p859-866 (2001)

Novelty of the claims is beyond doubt.

Inventive Step

The present invention relates to a method for preparing an acid addition salt of a specific piperazine derivative or a water adduct of said acid addition salt. The specific piperazine derivative is a compound of the generic formula 1 according to

the claims. Although the specific piperazine derivative is useful as a medicine in the form of the free base because the derivative has excellent effects of inhibiting ACAT and in the treatment of arteriosclerosis, a higher water-solubility and oral absorption can be obtained when the derivative is in the form of an acid addition salt rather than in the form of free base.

As discussed on page 3, lines 7 to 14 of the application as filed, 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide, for example, has a problem such that it crystallizes in the form of the free base, but its oral absorption is unsatisfactory because its crystals are not uniform and its physical stability and water solubility are too low. Therefore, it is desirable to provide an acid addition salt of the derivative. The importance of providing salts of pharmaceutical ingredients suitable as a candidate drug which has an industrial applicability and the problems associated therewith, are discussed in Reference 1.

However, since the specific piperidine derivative used in the present invention contains four basic nitrogen atoms which may add an acid, all forms of the salt, i.e. in case of a hydrochloride the tetrahydrochloride, trihydrochloride, dihydrochloride and monohydrochloride may be formed. The closest prior art D1 reflects this fact in that D1 states on page 18, lines 38/39: "The resulting compound (I) can be made into an acid addition salt(s) by a common method. It can also be prepared as solvate(s) with a solvent for the reaction or for the recrystallization, especially as a hydrate."

In drug development, it is necessary to select and provide the salt-form most suitable for a pharmaceutical ingredient as a defined substance. The closest prior art D1 does not disclose any common method in order to prepare acid addition salt(s) and solvate(s). The products obtained by addition of only acid, which represents a common method, has problems in terms of crystallization, thermal stability, hygroscopic property, etc, which indicates that the acid addition salts are mixtures of different products which are not desirable as pharmaceutical ingredient, cf. Table 1

on page 30 of the application as filed).

Accordingly, there has been strong demand for a preparation method making it possible to easily adjust the number of moles of an acid in an acid addition salt of a polyacidic basic compound to a number suited for the polyacidic basic compound as needed.

The difference between the subject matter of new claim 1 and the disclosure of D1 is based on the fact that D1 does not disclose a method which is characterized by controlling the number of moles of the acid to be added by reacting the piperazine derivative with an acid salt of pyridine.

Departing from the closest prior art D1, it is the problem of the invention to develop a preparation method which makes it possible to easily adjust the number of moles of an acid in an acid addition salt of the specific polyacidic basic compound defined by the claim, to a desired number in order to be able to reproducibly prepare defined acid addition salts in sufficient amounts and quality to select a pharmaceutical ingredient (crystal) to fulfill the most preferable condition by studying comprehensively chemical stability, physical stability (the degree of crystallization or hydration), the effect on the characteristics of drug product (degree of hardness, disintegration, dissolution) and the effect on the manufacture of pharmaceutical ingredient (molding, fluidity, packing) of pharmaceutical ingredient (especially, the crystal of acid salt) as pharmaceutical composition. This problem is left unsolved by the closest prior art D1.

This problem is solved by the method of new claim 1. The present invention provides a method for preparing an acid addition salt of a specific piperazine derivative (1) further defined by the claim, or a water adduct of said acid addition salt, wherein the number of moles of the acid to be added is controlled by reacting the piperazine derivative with an acid salt of pyridine.

The present invention is based on the recognition that only in the case of using an acid salt of pyridine, the number of moles of acid to be added into the specific piperidine derivative (1) can be controlled and the basic site(s) to which the acid is added can be also specified to obtain e.g. a uniform monohydrochloride or dihydrochloride, which were not available prior to the present invention.

Moreover, the present invention is also based on the recognition that acid addition salts obtained by the method of the present invention, for example, 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride 0.9-water adduct has a high degree of crystallinity, has no hygroscopicity, is excellent in thermal stability without being accompanied with any substantial weight change by dehydration, dehydrochlorination and/or the like, does not develop the problem of polymorphism, and is free from the influence of any residual of hydrochloric acid, so that said compound is a preferred acid addition salt and is useful as a pharmaceutical ingredient. As shown by Table 1 on page 30 of the present application, 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride 0.9-water adduct according to the present invention had a high degree of crystallinity, had no hygroscopicity, was excellent in thermal stability without any substantial weight change resulting from dehydration, dehydrochlorination and/or the like, did not develop the problem of polymorphism, was free from the influence of any residual of hydrochloric acid, and therefore, was a preferred acid addition salt as compared to acid addition salts obtained by other methods.

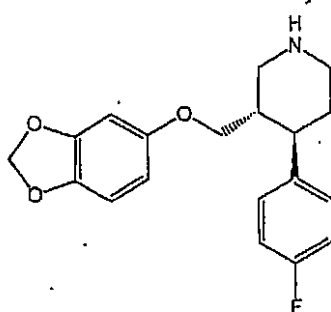
Finally, the present invention is also based on the recognition that the use of an acid salt of pyridine relatively weakens the acidity of the acid, and substantially lessens the problems of the conventional method such as the decomposition, the formation of impurities and the like by a localized pH reduction in a system due to the addition of a strong acid.

Accordingly, the present invention also provides a uniform monohydrochloride or dihydrochloride of the specific piperidine derivatives, crystals thereof, or water adducts of the crystal or compound. In these specified piperidine derivatives in which the number of moles of acids is controlled to one or two, they have very high degree of crystallization, low hygroscopicity and excellent thermal stability and no crystal modification caused by dry, anhydration or dehydrochloride when formulating drug and no change of its weight associated with crystal modification (cf. Table 1, Figs 13-24).

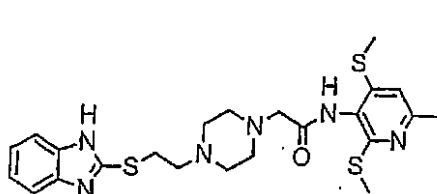
It must now be evaluated if there is any hint or suggestion in the prior art which would be able to render obvious the problem-solution relationship of the present invention departing from the closest prior art D1. It is submitted that this is not the case for the following reasons:

W000/32593

1. D2 relates to paroxetine hydrochloride. However, the paroxetine has the following chemical structure and has one basic site, whose structure is very different from the compound of the present invention. Therefore, the problems addressed by the present invention cannot arise in case of D2. Therefore, the skilled person would have no incentive to consider D2 when confronted with the objective problem of the present invention departing from the closest prior art D1.



2. In addition, D2 discloses that the desired monohydrochloride can be obtained by using alkylamine hydrochloride, ammonium chloride and the like other than pyridine hydrochloride. The present inventors applied ammonium chloride and dimethylamme hydrochloride to the present compound (i.e., 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin -1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide, as follows).



As a result, the desired crystal of monohydrochloride was not obtained by the above method. Therefore, it is not operable to precipitate a desired crystal by the use of antecedent similar to the present invention. In fact, the problems relating to the expectation of success in the context of providing a specific salt of a pharmaceutical ingredient may be illustrated by the case of ritonavir as discussed in Reference 2. Accordingly, in recent years, in the marketed crystalline drug, a crystal polymorph suddenly occurred during manufacturing process and the drug has been discontinued. The affair was immeasurable damage for the patients who had taken the drug as well as for society. This case shows the importance of crystal and represents the difficulty in making of prediction in this field.

It is respectfully believed that the application now on file is allowable. If this should not be the case an informal interview is requested or, if necessary, formal oral proceedings. Any further amendment to the description is postponed until the allowable wording of the claim is known.

WÄCHTERSCHÄUSER & HARTZ

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Erhardtstraße 27
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November 25 , 2009

Re: European Patent Application
No.: 04 715 495.0 - 2101
Kowa Company, Ltd.
Our Ref.: EA-PCT-13415

Response to the Communication dated August 14, 2009

A new set of claims 1 to 12 is filed wherein the subject matter of new claims 11 and 12 is now directed to 2- [4- [2- (benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof, and wherein the wording of claim 12 has been amended in accordance with the replacement pages as filed with our letter of September 16, 2005.

Comparative Tests in support of inventive activity of new claims 11 and 12 are filed in the form of a DECLARATION under 37 C.F.R §1.132 which was previously filed in the parallel proceedings before the USPTO.

Inventive Step of New Claims 11 and 12

D1 discloses the preparation of 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis-(methylthio)-6-methyl-3-pyridyl]acetamide dihydrochloride.

The difference between the subject matter of new claims 11 and 12 and the disclosure of D1 is that D1 does not disclose the specific monohydrochloride compound and product or water adducts thereof as claimed in new claims 11 and 12, respectively.

Starting out from the closest prior art D1, it is the problem of the invention to provide 2-[4-[2-(benzimidazol-2-ylthio)ethyl] piperazin-1-yl]-N-[2,4-bis-(methylthio)-6-methyl-3-pyridyl]acetamide with improved pharmacological properties including high crystallinity and high stability.

This problem is solved according to the invention with the specific monohydrochloride or water adducts thereof as defined by claims 11 and 12.

The solution according to the invention is demonstrated by the Comparative Tests enclosed herewith. In the Comparative Tests, the dihydrochloride of (benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl] acetamide as disclosed by the closest prior art D1 is compared to the monohydrochloride 0.9-water adduct according to the present invention. Moreover, the tetrahydrochloride and the free base are also compared to the compounds as claimed.

As shown by the enclosed DECLARATION, the physical and chemical properties of the claimed monohydrochloride compounds are surprisingly superior to the properties of the dihydrochloride and also with regard to the corresponding tetrahydrochloride compound or the free base.

Specifically, the dihydrochloride of D1 has almost no crystallinity at all as evidenced by the broad diffraction peaks in the X-ray diffraction spectrum of the dihydrochloride. Moreover, the dihydrochloride is highly unstable as evidenced by the water and HCl loss leading to a gradual reduction of mass with increased temperature in the TG-DSC spectrum of the dihydrochloride. The instability affects the physical properties

of the dihydrochloride in that the pH of a composition made with the dihydrochloride cannot be reliably predicted. Moreover, it will be difficult to determine a uniform dose of the active compound in view of the decomposition to be expected due to the instability of the dihydrochloride.

On the other hand, the monohydrochloride of the present invention is excellent both with regard to crystallinity and with regard to stability as evidenced with the X-ray diffraction spectrum and the TG-DSC-spectrum of the monohydrochloride in the DECLARATION. The superior chemical and physical properties of the monohydrochloride of the present invention are the basis for superior pharmacological properties as compared to any salt or base shown in the Table of the DECLARATION. Therefore, the pH and the dose of the specific monohydrochloride of the present invention may be reliably provided and predicted contrary to the dichloride known from the closest prior art D1.

It must now be evaluated if there is any hint or suggestion in the prior art which would be able to render obvious the problem-solution relationship of the present invention departing from the closest prior art D1. It is submitted that this is not the case for the following reasons:

1. None of the cited prior art references discloses a method which makes it possible to easily adjust the number of moles of an acid in an acid addition salt of the specific polyacidic basic compound defined by the claim. Therefore, none of the cited references enables the skilled person to prepare the specific monohydrochloride of the present invention.
2. Moreover, there is nothing in the prior art which would suggest that it is possible to provide 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis-(methylthio)-6-methyl-3-pyridyl]acetamide with improved pharmacological properties including high crystallinity and high stability by conceptually moving from the dihydrochloride to the monohydrochloride or a

water adduct thereof according to the present invention. The prior art cannot even be used to derive the existence of a defined monochloride, let alone the properties of the compound of the present invention.

It is respectfully believed that the application now on file is allowable. If this should not be the case an informal interview is requested or, if necessary, formal oral proceedings. Any further amendment to the description is postponed until the allowable wording of the claim is known.

Respectfully submitted,



Nikolaus F. Hartz
European Patent Attorney

Encl.

New claims 1 to 12;

Comparative Tests in the form of a DECLARATION;

Docket No.: 276446US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

GROUP: 1624

Kimiyuki SHIBUYA, et al.

SERIAL NO: 10/545,200

EXAMINER: JARRELL, N.

FILED: August 11, 2005

FOR: PROCESS FOR PRODUCING ACID ADDUCT SALT OF POLYACIDIC
BASE COMPOUND

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes Kimiyuki Shibuya who deposes and states:

1. That I am a graduate of Tohoku University and received a BS degree in 1979, an MS degree in 1981 and a Ph. D. degree in 1994.
2. That I have been employed by KOWA COMPANY, LTD., for 28 years as a researcher in the field of Medicinal and Organic Chemistry.
3. That I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.
4. That the following experiments were carried out by me or under my direct supervision and control.
5. The compound of Example 1 in the present specification which is a monohydrochloride of formula (1) was compared to the tetrahydrochloride and dihydrochloride of Shibuya, Example 32.
6. The base compound of formula (1) corresponding to that in Example 1 on page 21 of the specification is:

2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide.

7. Table A: Comparison of physical properties of the monohydrochloride of the invention with the same compound as tetrahydrochloride, dihydrochloride or as a base compound.

Example 1

Salt	Monohydrochloride 0.9-water adduct (invention)	Tetrahydrochloride 2-water adduct	Dihydrochloride Ex 32 of P1	Base compound
Melting point (°C)	194-196	193-196	214-218	92-95
Powder X-ray	Crystallinity	Low crystallinity	Non crystallinity	Low crystallinity
TG	No change until decomposition	Gradual removal of water and HCl	Gradual removal of water and HCl	No change
DSC/DTA	1 peak at 194°C	1 peak at 188°C	Non peak	1 peak at 104.5°C

8. As summarized above, the monohydrochloride of the invention is crystalline (see monohydrochloride powder X-ray diffraction pattern below), exhibits no change until decomposition (see monohydrochloride TG-DSC measurements below).

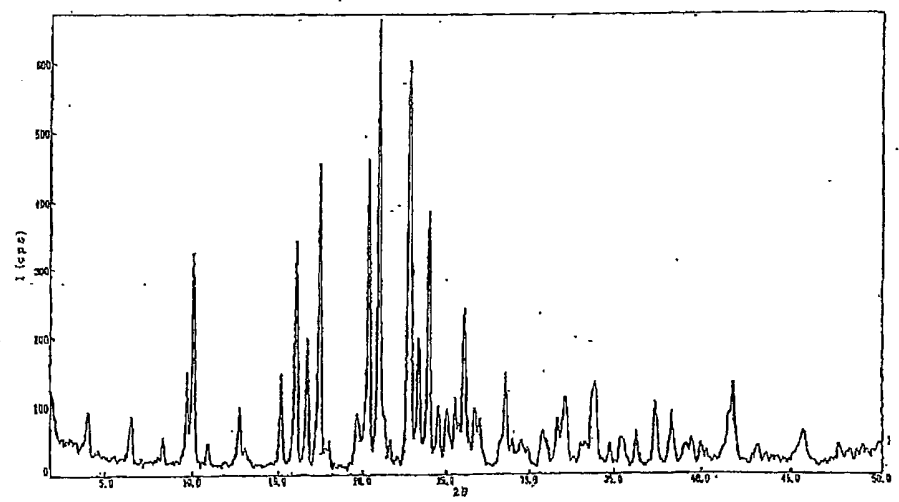
The dihydrochloride salt, which corresponds to the compound of Shibuya, has extremely low or no crystallinity (see dihydrochloride powder X-ray diffraction pattern below which lacks sharp peaks). Moreover, the dihydrochloride salt exhibits instability, because water and HCl are gradually removed (see dihydrochloride TG-DSC measurements which show gradual reduction of mass due to loss of water and HCl with increasing temperature).

The tetrahydrochloride salt and the base compound both exhibit low crystallinity as apparent from their respective powder X-ray diffraction patterns. The tetrahydrochloride salt is unstable based on TG-DSC analysis, undergoing gradual removal of water and HCl with increasing temperature.

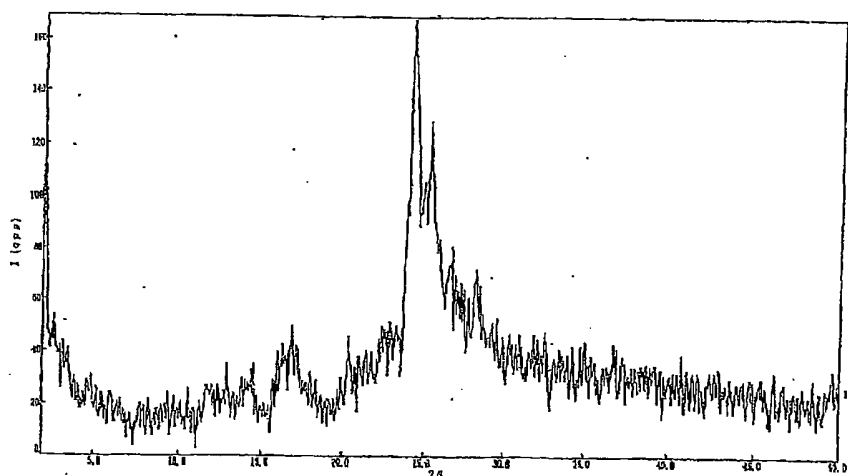
As evident from Table A, only the monohydrochloride salt of the invention exhibits a high degree of crystallinity and has high stability as determined by TG-DSC measurements.

9. The raw data summarized in Table A are provided below.

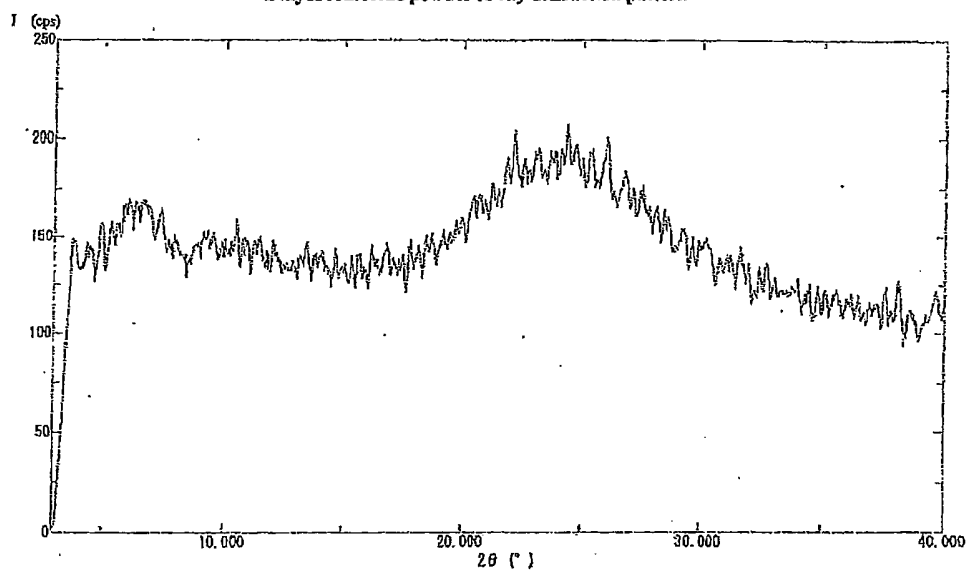
Monohydrochloride powder X-ray diffraction pattern

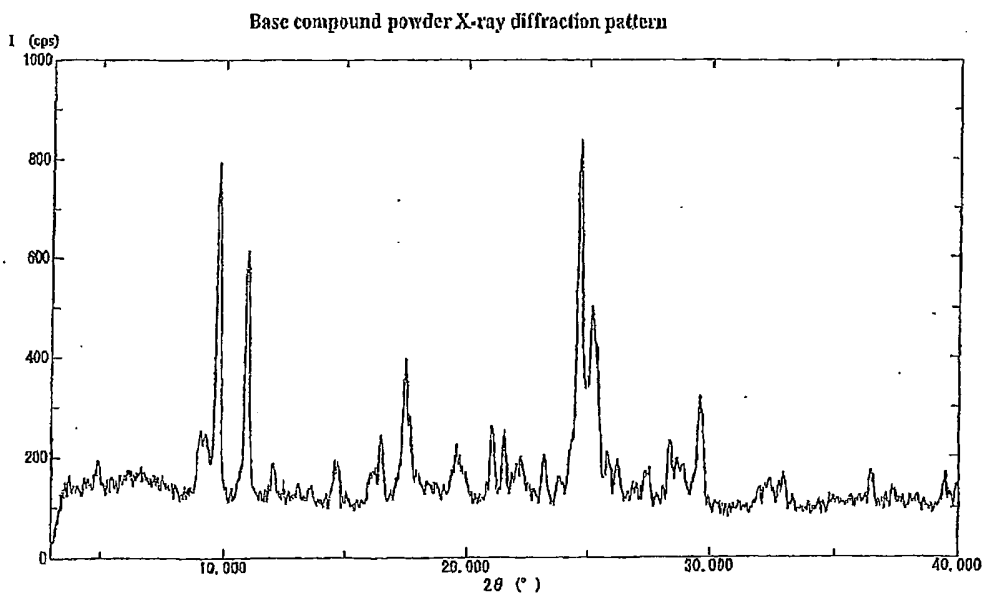


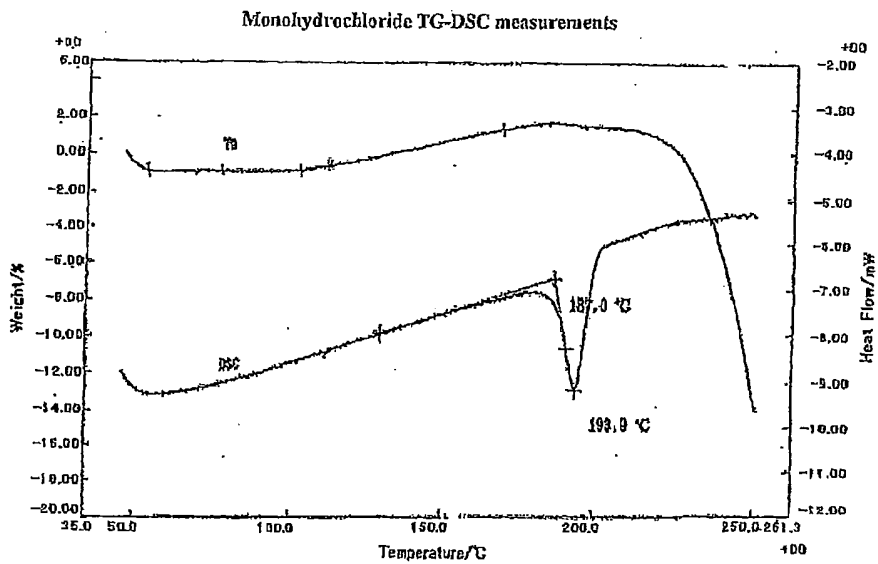
Tetrahydrochloride powder X-ray diffraction pattern



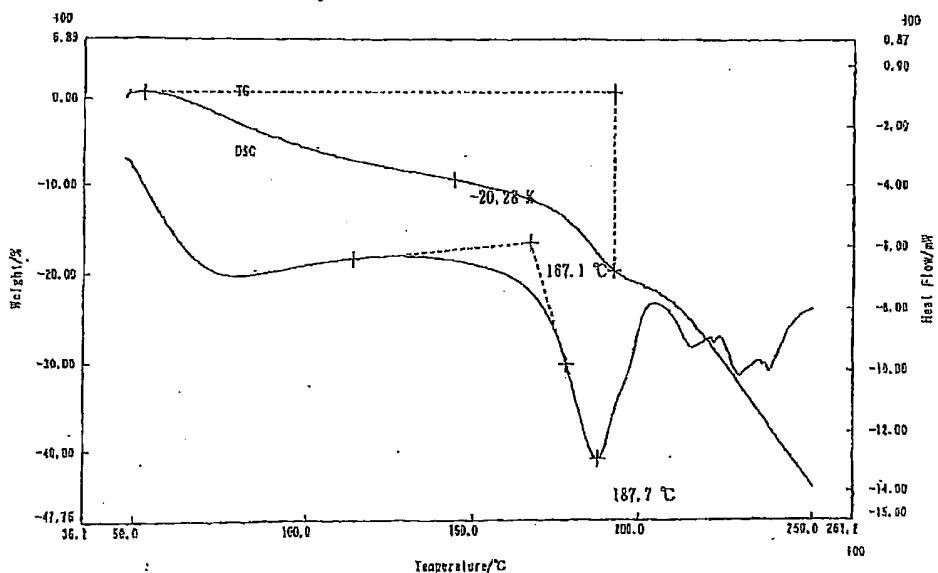
Dihydrochloride powder X-ray diffraction pattern

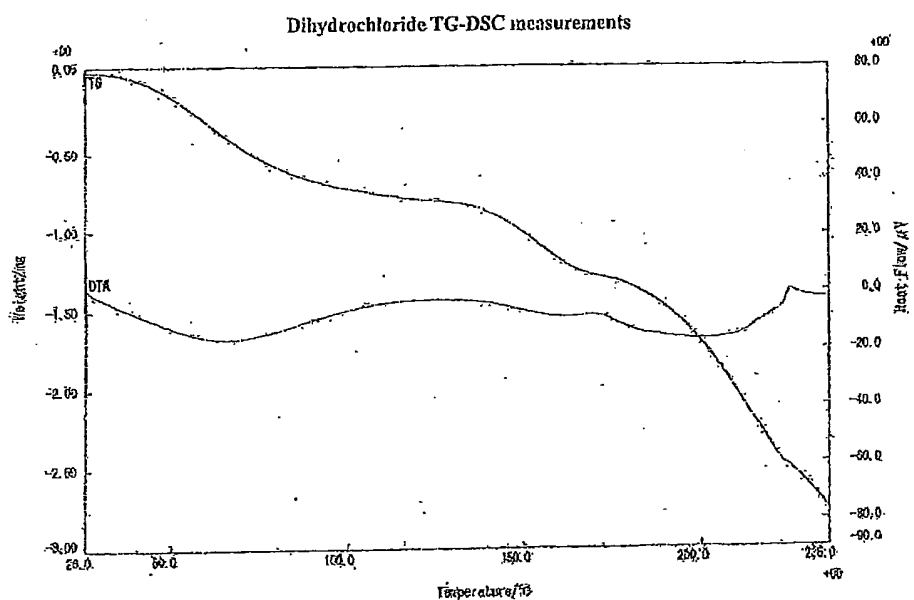


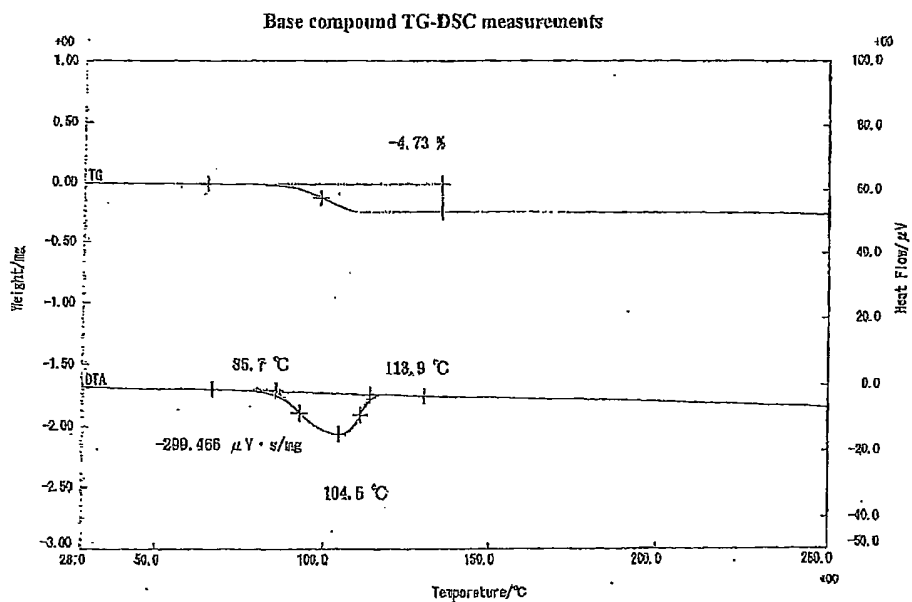




Tetrahydrochloride TG-DSC measurements







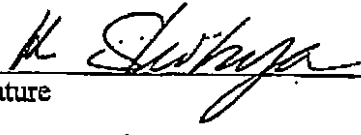
10. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

11. Further deponent saith not.

Customer Number

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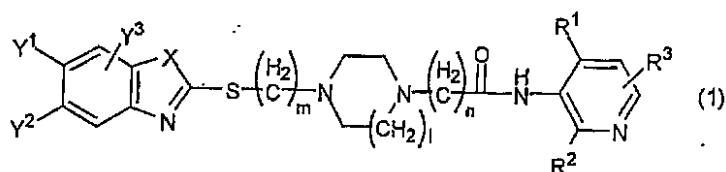
Tel. (703) 413-3000
Fax. (703) 413-2220
(OSM/MN 05/06)


Signature

March 10, 2009
Date

NEW CLAIMS

1. A method for preparing an acid addition salt of a piperazine derivative represented by the following formula (1) or a water adduct of said acid addition salt, which is characterized by controlling the number of moles of the acid to be added by reacting the piperazine derivative with an acid salt of pyridine:



wherein

X represents -NH-, an oxygen atom or a sulfur atom,

Y¹, Y² and Y³

each independently represent a hydrogen or halogen atom or a lower alkyl or lower haloalkyl group,

R¹, R² and R³

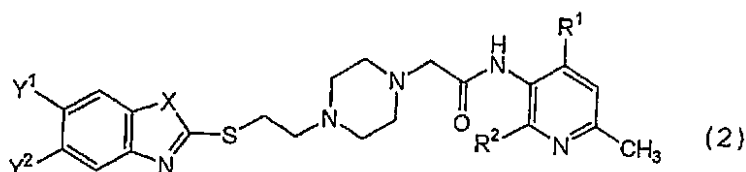
each independently represent a hydrogen or halogen atom or a lower alkyl, lower haloalkyl, lower alkylthio, lower haloalkoxy or lower alkoxyalkoxy group,

l denotes an integer of from 1 to 2,

m denotes an integer of from 2 to 4, and

n denotes an integer of from 1 to 3.

2. The method for preparing an acid addition salt of a piperazine derivative described in claim 1, wherein said piperazine derivative is represented by the following formula (2):



wherein

X represents -NH-, an oxygen atom or a sulfur atom,

Y¹ and Y²

each independently represent a hydrogen or halogen atom or a trifluoromethyl group,

R¹ and R²

each independently represent a methyl, trifluoromethyl, methylthio, trifluoroethoxy or methoxyethoxy group.

3. The method for preparing an acid addition salt of a piperazine derivative or a water adduct of said acid addition salt described in claim 1, wherein said piperazine derivative is
2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl] acetamide,
2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(benzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(benzothiazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,6-dimethyl-4-trifluoromethyl-3-pyridyl]acetamide, 2-[4-[2-(5-trifluoromethylbenzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide, or
2-[4-[2-(benzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2-(2methoxyethoxy)-4-(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl] acetamide.
4. The method for preparing an acid addition salt of a piperazine derivative or a water adduct of said acid addition salt described in claim 1, wherein said piperazine derivative is
2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide or
2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl] acetamide.

5. The method for preparing an acid addition salt of a piperazine derivative or a water adduct of said acid addition salt described in any one of claims 1-4, wherein the acid in said acid salt of pyridine is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, sulfurous acid, nitrous acid, hydrobromic acid, hydroiodic acid, acetic acid, butyric acid, stearic acid, oxalic acid, maleic acid, succinic acid, fumaric acid, citric acid, lactic acid, tartaric acid, malic acid, mandelic acid, salicylic acid, pamoic acid, pantothenic acid, gluconic acid, ethanedisulfonic acid, benzenesulfonic acid, paratoluenesulfonic acid, methanesulfonic acid, glutamic acid, aspartic acid, trifluoroacetic acid, and tannic acid.
6. The method for preparing an acid addition salt of a piperazine derivative described in any one of claims 1-5, wherein said acid salt of pyridine is a pyridine hydrochloride.
7. The method for preparing an acid addition salt of a piperazine derivative or a water adduct of said acid addition salt described in claim 1, wherein said piperazine derivative is
2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(benzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide,
2-[4-[2-(benzothiazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,6-dimethyl-4-trifluoromethyl-3-pyridyl]acetamide,
2-[4-[2-(5-trifluoromethylbenzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide, or
2-[4-[2-(benzoxazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2-(2-methoxyethoxy)-4-(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide; and said acid salt of pyridine is a pyridine hydrochloride.
8. The method for preparing an acid addition salt of a piperazine derivative or a water

adduct of said acid addition salt described in claim 1, wherein said piperazine derivative is

2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide or

2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl] acetamide;

and said acid salt of pyridine is a pyridine hydrochloride.

9. The method described in claim 1, wherein said piperazine derivative is 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide; said acid salt of pyridine is a pyridine hydrochloride; and said acid addition salt of a piperazine derivative is 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof.
10. The method described in claim 1, wherein said piperazine derivative is 2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl] acetamide; said acid salt of pyridine is a pyridine hydrochloride; and said acid addition salt of a piperazine derivative is 2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof.
11. 2-[4-[2-(Benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof.
12. 2-[4-[2-(Benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride crystal or a water adduct thereof.

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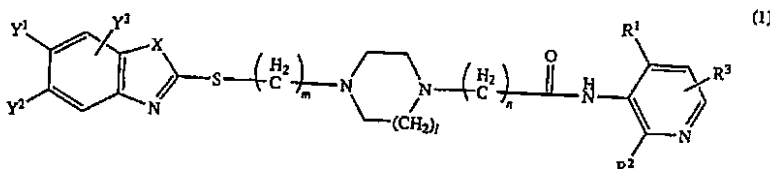
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IR(KBr)cm⁻¹: 3432, 1686, 1593, 1507, 1454, 1170, 1137.
¹H-NMR(400 MHz, CD₃CN) δ: 2.38 (3H, s), 2.92-3.26 (8H, m), 3.31 (3H, s), 3.42-3.59 (4H, m), 3.62 (2H, t, J=4.9 Hz), 3.72-3.84 (2H, m), 4.38 (2H, t, J=4.9 Hz), 4.54 (2H, q, J=8.3 Hz), 6.61 (1H, s), 7.28-7.36 (2H, m), 7.54 (2H, dd, J=2.2, 5.6 Hz), 8.19 (1H, br).

Elemental analysis for C₂₆H₃₃ClF₃N₅O₅S.0.4H₂O
 Calculated: C, 49.78; H, 5.43; N, 11.16; Cl, 5.65.
 Found: C, 49.76; H, 5.31; N, 11.25; Cl, 5.78.

The invention claimed is:

1. A method for preparing a monohydrochloride acid addition salt of a piperazine derivative or a water adduct of said monohydrochloride acid addition salt comprising:
 reacting a piperazine derivative with an acid salt of pyridine thus forming a monohydrochloride acid addition salt of said piperazine derivative;
 wherein said piperazine derivative is characterized by formula (I):



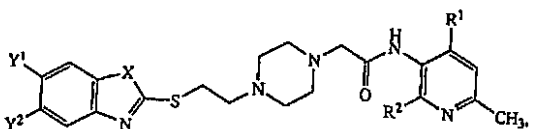
wherein

X represents —NH—,

Y¹, Y² and Y³ each independently represent a hydrogen or halogen atom or a lower alkyl or lower haloalkyl group,

R¹, R² and R³ each independently represent a hydrogen or halogen atom or a lower alkyl, lower haloalkyl, lower alkylthio, lower haloalkoxy or lower alkoxyalkoxy group, 1 denotes an integer of from 1 to 2, m denotes an integer of from 2 to 4, and n denotes an integer of from 1 to 3.

2. The method of claim 1, wherein said piperazine derivative is represented by formula (2):



wherein X represents —NH—, Y¹ and Y² each independently represent a hydrogen or halogen atom or a trifluoromethyl group, R¹ and R² each independently represent a methyl, trifluoromethyl, methylthio, trifluoroethoxy or methoxyethoxy group.

3. The method of claim 1, wherein said piperazine derivative is selected from the group consisting of:

2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide
 and

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2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide.

4. The method of claim 1, wherein said acid salt of pyridine is prepared from 1.0 to 1.5 equivalents of pyridine to 1 equivalent of hydrochloric acid.

5. The method of claim 1, wherein said acid salt of pyridine is a pyridine hydrochloride.

6. The method of claim 1, wherein said piperazine derivative is:

2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide, or

2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide; and

said acid salt of pyridine is a pyridine hydrochloride.

7. The method of claim 1, wherein said piperazine derivative is 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide;

said acid salt of pyridine is a pyridine hydrochloride; and said acid addition salt of a piperazine derivative is 2-[4-[2-(benzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof.

8. The method of claim 1, wherein said piperazine derivative is 2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide;

said acid salt of pyridine is a pyridine hydrochloride; and said acid addition salt of a piperazine derivative is 2-[4-[2-(5,6-difluorobenzimidazol-2-ylthio)ethyl]piperazin-1-yl]-N-[2,4-bis(2,2,2-trifluoroethoxy)-6-methyl-3-pyridyl]acetamide monohydrochloride or a water adduct thereof.

9. The method of claim 1, further comprising precipitating crystals of said monohydrochloride acid addition salt and recovering the crystals; and, optionally, washing and/or drying the recovered crystals.

10. The method of claim 1, wherein said reacting occurs in an anhydrous organic solvent.

11. The method of claim 1, wherein said reacting occurs in an organic solvent containing water.

12. The method of claim 1, wherein said reacting occurs in an organic solvent selected from the group consisting of methanol, ethanol, isopropanol, dioxane, tetrahydrofuran, acetone and acetonitrile.

13. The method of claim 1, wherein said monohydrochloride acid addition salt of a piperazine derivative or said water adduct of said monohydrochloride is prepared from 1.0 to 3.0 equivalents of pyridine hydrochloride.

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