Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**ASTRAZENECA AB.**- Solicitud de Patente de Invención para **"FORMA CRISTALINA"**.-Clase A61.-Expediente número **00-091.382.-**

1. Me refiero a mi solicitud arriba nombrada de 29 de Noviembre de 2000.

2. Anexos me permito presentar a usted:

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber:

(a) Copia legalizada, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud sueca número 9904417-4 de 3 de Diciembre de 1999 debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 570402 de 22 de Noviembre de 2000, junt con su Traducción Oficial correspondiente a las legalizaciones y reivindicaciones también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 483132 de 30 de N viembre de 2000;

(b) Copia legalizada, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado

respecto de la cual reclamo prioridad, a saber la solicitud sueca número 0001422-5 de 17 de Abril de 2000 debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 570403 de 22 de Noviembre de 2000, junto con su Traducción Oficial correspondiente a las legalizaciones y reivindicaciones también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 570402 de 22 de Noviembre de 2000;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid, quien elaboró la traducción de las legalizaciones y reivindicaciones de las solicitudes suecas número 9904417-4 y 0001422-5 de 3 de Diciembre de 1999 y 17 de Abril de 2000 respectivamente;

(3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representad , de sus derechos sobre el mismo, debidamente legalizado hasta por el 570416 de 22 de Noviembre de 2000; y

(4) Traducción Oficial No. 322, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 394494 de 27 de N viembre de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

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EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DE MINISTERIO DE RELACIONES EXTERIORES.

HACE CONSTAR

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE ME TENIDO A LA VISTA.
SANTAFE DE BOGOTA 23 DIC 2000
JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

Que el señor Gabriel Rueda, se encuentra debidamente registrado ante este Ministerio, como traductor e intérprete oficial para los idiomas INGLES -ESPAÑOL, ESPAÑOL - INGLES.

Para efectos de ésta certificcción el interesado presentó copia autenticada de la certificación del Ministerio de Justicia acerca de la vigencia de la resolución 5996 1982.

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE ME TENIDO A LA VISTA.
SANTAFE DE BOGOTA 21 AGO. 1998

Dada en Santafé de Bogotá, D.C., a los diez y nueve días (19) del mes de diciembre de 1994.

Nelson Sánchez Torres
Jefe Area de Legalizaciones

COMO NOTARIO SEXTO ENCARGADO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE ME TENIDO A LA VISTA
01 JUL 1998
PABLO MENDEZ BARAJAS

COMO NOTARIO SEXTO ENCARGADO
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE ME TENIDO A LA VISTA.
SANTAFE DE BOGOTA 01 SET 2000

NST/gtm.

República de Colombia

Ministerio de Justicia y del Derecho

33
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COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 13 DIC 2000
JULIAN MANUEL BOTERO ZAMBRANO
NOTARIO

EL SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cédula de ciudadanía No. 17.124.145 expedida en Bogotá. Que dicha resolución se encuentra vigente en la fecha.

A solicitud del interesado, en Santafé de Bogotá D.C., a los 17 días del mes de noviembre de 1994.

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 17 AGO. 1998
PABLO MENDEZ BARAJAS
NOTARIO (E)

JORGE LUIS SABOGAL SABOGAL
SECRETARIO GENERAL

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 SET. 2000

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 JUL 1998
PABLO MENDEZ BARAJAS
NOTARIO (E)

LMR/mmc

3234

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA,

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 19 DIC. 2000
JUAN MANUEL BOTERO MEDINA
NOTARIO

C E R T I F I C A :

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía número 17.124.145 de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, se encuentra VIGENTE.

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 01 SET. 2000
JUAN MANUEL BOTERO MEDINA
NOTARIO

Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre mil novecientos noventa y cuatro (1994).

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 27 AGO. 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

MARIA INES RODRIGUEZ TORRES
SECRETARIA

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 03 DIC. 1998
PABLO MEDINA GARAVITO

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 01 JUL 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 23 NOV. 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

crm./

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Astra Zeneca AB 2285-ICO

REF: LLC-117-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

PRV

Patent-OCH Registreringsverket

CERTIFICACION

Se certifica que anexo se encuentra fiel copia de los documentos tal y como fueron radicados originalmente ante la Oficina de Registros y Patentes en relación con la siguiente solicitud de patente.

La solicitud se presentó originalmente en inglés.

(71) Solicitante: AstraZeneca AB, Södertälje SE
(21) Número de Solicitud de Patente. 9904417-4
(86) Fecha de presentación: 1999-12-03

Estocolmo, 2000-10-18

Por y en representación de la Oficina de Registros y patentes.
Therese Friberger (Hay firma y sello)
Derechos: 170

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

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La suscrita Anne-Marie Bonde, Notario Público de la Ciudad de Estocolmo, Suecia, certifica que THERESE FRIBERGER autorizado para firmar en nombre de la PRV, REGISTRO NACIONAL DE LA PROPIEDAD INDUSTRIAL DE SUECIA ha otorgado y firmado el documento que antecede.

Derechos: 250 Coronas

Estocolmo, 2000-10-26

Hay firma y Sello

CONSULADO DE COLOMBIA EN ESTOCOLMO, SUECIA

Fecha: 2000-10-30 No. 003615

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aquí por Anne-marie Bonde, Notario Público de la Ciudad de Estocolmo, Suecia.

Firmado y Sellado por

MARIA SMITH RUEDA

Encargada de las Funciones Consulares

MINISTERIO DE RELACIONES EXTERIORES

No. *570402*

Fecha: Noviembre 22, 2000.

MARIA SMITH RUEDA, cuya firma aparece en el documento desempeña las funciones indicadas.

Jefe de Legalizaciones, Santafé de Bogotá D.C.

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

MINISTERIO DE RELACIONES EXTERIORES

483132

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE HACE RESPONSABILIDAD DEL TEXTO

2001 NOV 30

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

PVR99-12-03 **ASTRA**

Solicitante: **Astra Aktiebolag**
S-151 85 Södertälje
Suiza

Título: **FORMA CRISTALINA**

Referencia: H 2285-1

Inventores: Maria Boije

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-83
MINISTERIO DE JUSTICIA

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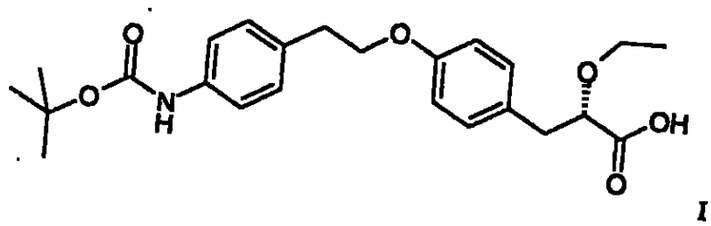
REIVINDICACIONES **PRV 99-12-03**

1. Una forma cristalina de la composición ácido propanoico 3-{4-[2-(4-*tert*-butoxicarbonilaminofenil) etoxi] fenil}-(S)-2-etoxi. que se aprecia en la formula I a continuación



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o una de sus sales o solvatos farmacéuticamente aceptables.

2. Una forma cristalina según se describió en la reivindicación 1 que es sustancial o esencialmente libre de solventes.

3. Una forma cristalina según se describió en la reivindicación 2 que se caracteriza por tener un punto de fusión entre 102 y 112°C.

4. Una forma cristalina según se describió en la reivindicación 2 que se caracteriza por cuanto tiene un patrón de difracción de polvos de rayos X que contiene picos específicos de alta intensidad a 9.3, 5.5, 4.89, 4.83, 4.67, 4.22. 3.82 y 3.62A.

5. Una forma cristalina según se describió en la reivindicación 4 que se caracteriza por cuanto tiene un

patrón de difracción de polvos de rayos X con picos adicionales específicos de intensidad relativa menor con respecto de los primeros picos en los puntos 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 y 2.59A.

6. Una forma cristalina de una composición de la formula I, según se describió en una de las reivindicaciones 1 a 5, para utilizarse en forma de medicamento.

7. Una formulación farmacéutica que comprende una forma cristalina de una composición de la formula I, según se describió en una de las reivindicaciones 1 a 5, y uno de sus adyuvantes, diluyentes o portadores farmacéuticamente aceptables.

8. La utilización de una forma cristalina de una composición de la formula I, según se definió en una de las reivindicaciones 1 a 5, para la preparación de un medicamento para el tratamiento o profilaxis de una condición patológica del metabolismo, incluyendo el síndrome de resistencia a la insulina.

9. El uso de una sustancia según se definió en una de las reivindicaciones de 1 a 5 para la producción de un medicamento para utilizarlo en el tratamiento de trastornos metabólicos.

10. Un método para el tratamiento o profilaxis de condiciones asociadas con reducción de la sensibilidad a la

insulina, el cual comprende la administración de una cantidad terapéuticamente eficaz de una composición de acuerdo con una de las reivindicaciones 1 a 5, a un paciente que presente tal reducción de sensibilidad a la insulina.

11. Un método para el tratamiento o profilaxis de la dislipidemia, diabetes mellitus tipo II, hiperglicemia, hiperinsulinemia, hipertensión arterial y/o obesidad abdominal, donde dicho método comprende la administración de una cantidad terapéuticamente eficaz de una composición de acuerdo con una de las reivindicaciones 1 a 5 a un paciente que necesite de dicho tratamiento o profilaxis.

12. Un proceso para la preparación de una forma cristalina de una composición de la formula I que comprende la cristalización de la composición de dicha formula I.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por **GABRIEL RUEDA CHADID (Traductor Oficial)**. Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Bogotá D.C., Noviembre 28, 2000.

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

FOR ILLEGIBLE PURPOSES

2285-1 CO 99

leg. 39

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

PATENT- OCH REGISTRERINGSVERKET

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

(21) *Patentansökningsnummer* *9904417-4*
Patent application number

(86) *Ingivningsdatum* *1999-12-03*
Date of filing

Stockholm, 2000-10-18

För Patent- och registreringsverket
For the Patent- and Registration Office

Therese Friberger

Therese Friberger

Avgift
Fee *170:-*

La infrascrita Anne-Marie Bonde, Notario Público de Estocolmo, Suecia, certifica que

THERESE FRIBERGER,

autorizado para firmar en nombre de la PRV, REGISTRO NACIONAL DE LA PROPIEDAD INDUSTRIAL DE SUECIA, ha otorgado y firmado el documento que antecede.

Derechos 250 - Estocolmo, 2000-10-26
Coronas Por oficio:

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

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+46 8 782 25 00
Vx 08-782 25 00

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PATOREG S

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08-666 02 86

EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha 2000 -10- 30 No: 003615

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aqui por Ana María Baudet Notaria Pública Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre ..... dólares US$ 4
Derechos Consulares ..... dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2000 NOV 22 P 3:44

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

5140

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40

Applicant: **Astra Aktiebolag**
S-151 85 Södertälje
Sweden

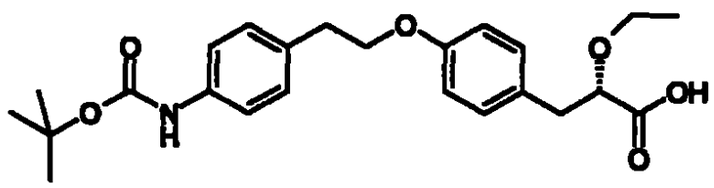
Title: **CRYSTALLINE FORM**

Reference: **H 2285-1**

Inventors: **Maria Boije**

Crystalline Form

The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown by the formula I (set out below)



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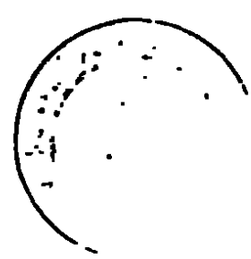
or a pharmaceutically-acceptable salt thereof and any solvates of thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of the crystalline form of the compound, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing the crystalline form of the compound, or a solvate thereof, as active ingredient, as well as processes for the manufacture of the crystalline form of the compound, or a solvate thereof..

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance in obtaining a commercially viable manufacturing process, and also for subsequent manufacture of pharmaceutical formulations comprising the active compound.

Chemical stability, solid state stability, and shelf life of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and



Moreover, it is also important to be able to provide a drug in a form which is as chemically-pure as possible.

Amorphous materials may present significant problems in this regard. For example, such materials are typically difficult to handle and to formulate compared with crystalline forms, provide for unreliable solubility, and are often found to be unstable and chemically impure.

The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable, drug compositions, it is desirable, wherever possible, to provide drug in a substantially crystalline, and stable, form.

It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallisation behaviour of a compound will be, and this can usually only be determined empirically. The above compound is intended for therapeutic use in Insulin Resistance Syndrome (IRS), refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possible type II diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type II diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

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In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally well defined disease.

The present invention relates to a crystalline solid form of the compound of formula I. Significant advantages can arise when the compound of formula I can be isolated in a crystalline form, for example, in the manufacture of the compound to the purity levels and uniformity required for regulatory approval and for ease and uniformity of formulation.

We present as a feature of the invention a crystalline form of a compound of formula I, or a solvate thereof. In an alternative feature of the invention we present a crystalline form of a pharmaceutically-acceptable salt of the compound of formula I, or a solvate thereof.

We have isolated the compound of formula I as a crystalline solid which exists in a form which is substantially or essentially free of solvent (hereinafter referred to as the "anhydrous" form). Alternatively a solvated form may be formed, for example, a hydrated form. In a further alternative we have also isolated a crystalline form of the sodium salt of the compound of formula I.

By the use of the term "solvated" we include the term hydrated.

The crystalline form of the compound of formula I can be defined by reference to its melting point, powder X-ray diffraction pattern and single crystal X-ray data.

The melting point of the crystalline form of the compound of formula I generally depends on the level of purity and may be determined by conventional procedures well known in the art, for example, by differential scanning calorimetry (DSC). Typically, the compound of formula I has a melting point which is in the range 102-112°C, for example about 105-109°C, when it is substantially or essentially in the anhydrous form.

The crystalline form of the compound of formula I, when it is substantially or essentially in the anhydrous form, has an X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62Å. Additional specific peaks of lower relative intensity to the first peaks are at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59Å.

Crystalline compound of formula I may be obtained from a non-crystalline form of the compound of formula I, by crystallisation from a suitable solvent (including organic solvents, aqueous solutions and mixtures thereof), such as isooctane, butylacetate and toluene, or a mixture of solvents, such as a mixture of ethanol and water. To initiate crystallisation, seeding with crystalline compound of formula I may be required. Crystallisation of the compound from an appropriate solvent system may be achieved by attaining supersaturation, for example, by cooling, by solvent evaporation and or by the addition of an anti-solvent (a solvent in which the compound of formula I is poorly soluble, example of suitable anti-solvents include heptane and isooctane). Crystallisation temperatures and times will vary depending upon the concentration of the compound in solution, the solvent system used and the method of crystallisation adopted.

The crystalline forms of the compound of formula I may be isolated using techniques well known to those skilled in the art, for example, by decanting, filtration or centrifuging. Similarly the crystalline form may be dried in accordance with well known procedures.

Optional recrystallisation step(s) may be performed using the same or different solvent systems to reduce further impurities, such as amorphous material, chemical impurities or to convert the crystalline into a solvated/hydrated form or an anhydrous form.

A further feature of the invention is a process for the production of a crystalline form of a compound of formula I which comprises crystallising the compound of

Preferably the compound of formula I is crystallised directly from the reaction solution or may be crystallised from a subsequent solution.

A hydrate has 0.8 water molecule, per compound molecule, and upwards (80% hydrated). A hemi-hydrate has 0.4 water molecule, per compound molecule, and upwards (40%). An anhydrous form has 0.3 water molecule, per compound molecule, and downwards (30%). The above refers to crystal water, loose bound water may vary, for example 0-0.5 water molecule.

By the use of the term "substantially or essentially in the anhydrous form", we do not exclude the presence of some solvent, including water, within the crystal lattice structure. As described above solvent, including water, may also be present outside the crystal lattice structure. Therefore, the anhydrous form contains less than 0.3 water molecule, per compound molecule, preferably less than 0.1 water molecule, per compound molecule.

A feature of the invention is a crystalline form of a compound of formula I, as described above, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a crystalline form of a compound of formula I, as described above, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example

a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of the crystalline form of a compound of formula I, as described, above, that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.001 mg to 10mg of active agent compounded with an appropriate and convenient amount of excipient(s) which may vary from about 20 to about 99.99 percent by weight of the total composition. Dosage unit forms will generally contain about 0.0001 mg to about 1 mg of an active ingredient.

The invention also includes the use of the crystalline compound of the invention, as described above in the production of a medicament for use in:-

(i) treating dyslipidemia;

(ii) treating type II diabetes mellitus;

(iii) treating hyperglycaemia;

(iv) treating hyperinsulinaemia;

(v) treating hyperlipidaemia;

(vii) treating arterial hypertension; and/or

(viii) treating abdominal obesity.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring, preferably humans, such treatment an effective amount of a crystalline form of a compound of formula I, as described above.

The size of the dose for therapeutic or prophylactic purposes of a crystalline form of a compound of formula I will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and

the route of administration, according to well known principles of medicine. Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

A crystalline form of the compound of formula I may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a anti-diabetic, anti-hypertensive, diuretic or anti-hyperlipidaemic agent.

Crystalline forms prepared in accordance with the Example(s) below showed essentially the same powder X-ray diffraction patterns and/or DSC themograms. It was clear when comparing the relevant patterns/thermographs (allowing for experimental error) that the same crystalline form had been formed. DSC onset temperatures may vary in the range ±5°C (for example ±2°C), and powder X-ray diffraction pattern distance values may vary in the range ±2 on the last decimal place.

Synthesis of 3-[4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid

Ethyl 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoate

Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (250g, 1.05 mol, 1.0 eq) was dissolved in dimethysulphoxide (DMSO) (1000 ml). When a homogenous solution was formed, NaOH (s), beads, 20-40 mesh (48.2 g, 1.21 mol, 1.15 eq) was added. 1-(4-Methyl)phenylsulfonyloxy-2-[(4-*tert*-butoxycarbonylamino)phenyl]ethane (431 g, 1.10 mol, 1.05 eq) was dissolved in DMSO (1000 ml). The DMSO solution of 1-(4-methyl)phenyl-sulphonyloxy)-2-[4-(*tert*-butoxycarbonylamino)phenyl]ethane was then added over 10 minutes at 20-25 °C to the solution of (S)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)-propanoate. The reaction mixture was then stirred for 1 hour. To fully convert ethyl (S)-2-ethoxy-3-(4-

hydroxyphenyl)-propanoate to ethyl 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoate an additional amount of 1-(4-methyl)phenylsulfonyloxy-2-[(4-*tert*-butoxycarbonylamino)phenyl] ethane (20 g, 0.05 mol, 0,05 eq) and NaOH (s), beads, 20-40 mesh (2.1 g, 0,05 mol, 0.05 eq) was added. The reaction mixture was stirred for another 3 hours. The mantle was then cooled to 10°C.

3-[4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid

NaOH (aq) 1M (1.15 l, 1.15 mol, 1.15 eq) was added to a solution of ethyl 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoate over 30 minutes at 19-23 °C. Stirring was continued for 1 hour, and then H_2O (4000 ml) was then added. The water layer was washed with methyl *tert*-butylether (3×2000 ml). The water layer was then acidified to pH 3 with $KHSO_4$ (aq) 1M (1.6 L, 1.6 mol, 1.6 eq). The acidic water solution was then extracted with ethylacetate (3×2000 ml). The ethylacetate-parts were put together and washed with H_2O (4×2000 ml). The ethylacetate solution was dried with $MgSO_4$ (90 g). The salts were filtered off and washed with ethylacetate (3×100 ml). The filtrate was evaporated to dryness. The oil residue (750 g) was dissolved in toluene (1750 ml). The solution was seeded with 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid and the crystallisation was continued for 30 minutes. Then isooctane (3500 ml) was added. The slurry was stirred for 15 minutes and then filtered. The solid was washed with toluene:isooctane 1:2 (400 ml) followed by water (300 ml). Drying at 40°C at reduced pressure yielded 382 g (0.89 mol) of 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid as a white powder.

Recrystallisation from Butylacetate & Isooctane

3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid (382 g, 0.89 mol, 1.0 eq) was dissolved in butylacetate (2100 ml) at 40°C. The

solution was cooled to -5°C and then seeded with 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid. The crystallisation started immediately. The mixture was cooled to –15°C over 1 hour. Isooctane (2010 ml) was then added to the slurry over 50 minutes. The slurry was stirred for another 10 minutes and then filtered off. The solid was then washed with cold butylacetate:isooctane 1:1 (1000 ml). The solid was dried using reduced pressure at 40°C, yielding 340 grams (0.79 mol) of 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid as a white powder.

Recrystallisation from Ethanol & H_2O

Two batches of 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid (680 g, 1.59 mol, 1.0 eq) were dissolved in ethanol (2100 ml) at 40°C. To the solution H_2O (1000 ml) was added over 20 minutes at 40°C. The solution was seeded with 3-[4-[2-(4-*tert*-butoxycarbonylamino-phenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid (0.3g). H_2O (4100 ml) was added over 70 minutes. The slurry was then cooled to 5°C over 100 minutes. The slurry was stirred for another 20 minutes and then filtered off. The solid was washed with cold ethanol:H_2O 2:5 (1500 ml). The solid was dried using reduced pressure at 55°C, yielding 667 grams (1.55 mol) 3-[4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxy propanoic acid as a white solid.

Melting Point Determination

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in: Höhne, G. W. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

DSC of the anhydrous form showed an endotherm with an extrapolated onset temperature of *ca* 107 °C (*ca* 112 J/g). Thermogravimetric analysis was performed

using a Mettler Toledo TGA850 instrument and showed a decrease in mass of *ca* 0.15% when the compound melts, followed by decomposition.

Powder X-ray Diffraction Pattern Determination

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in: Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley and Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. and Alexander, L. E. (1974), *X-Ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD.

The crystals of the anhydrous form were analysed by XRPD and the result is tabulated below in Table 1 (in which RI represents relative intensity), and shown in Figure 1. The diffractogram was measured with variable slits and without internal standard. The intensities are based on the intensities observed in a variable slit measurement without background subtraction. The relative intensities are less reliable, and instead of numerical values, the following definitions are used:

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3 %	w (weak)

Some additional weak or very weak peaks found in the diffractogram have been omitted from Table 1.

Table 1. X-ray powder diffraction data for the anhydrous crystalline form of the compound of formula I is shown in Figure 1.

d-value/Å	RI	d-value/Å	RI
14.4	s	3.42	m
9.7	m	3.36	m
9.3	vs	3.31	m
8.6	m	3.11	m
7.2	m	3.07	s
7.1	m	3.03	m
6.0	s	3.00	m
5.7	s	2.95	m
5.5	vs	2.90	m
5.2	m	2.84	m
4.99	s	2.79	m
4.89	vs	2.77	m
4.83	vs	2.59	s
4.67	vs	2.46	m
4.53	s	2.43	m
4.46	s	2.34	m
4.33	s	2.31	m
4.28	s	2.28	m
4.22	vs	2.24	m
4.05	m	2.20	m
3.99	s	2.17	m
3.90	m	2.11	m
3.82	vs	2.08	m
3.70	s	2.00	m
3.62	vs	1.96	m
3.54	s	1.91	m
3.47	s		

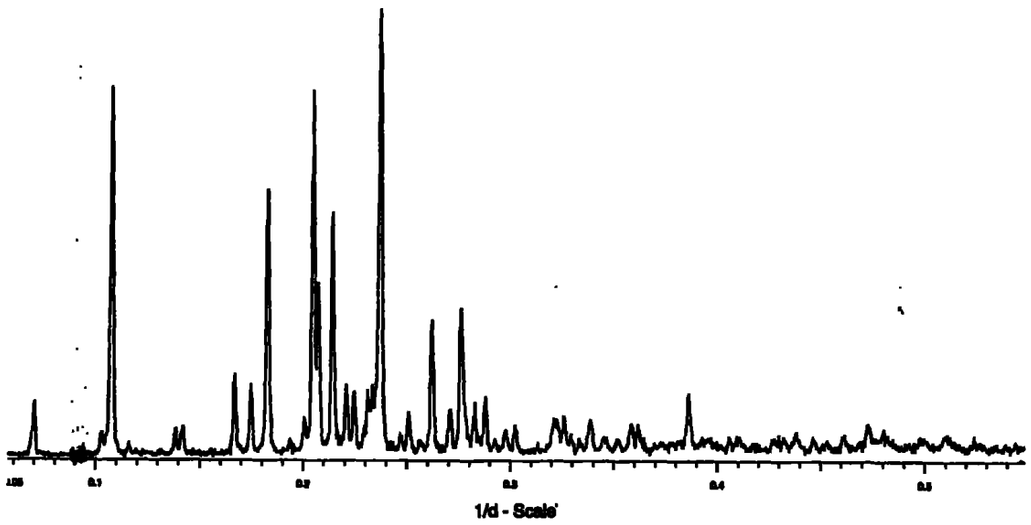
It will be understood that the d-values of the X-ray powder diffraction patterns may vary slightly from one machine to another and so the values quoted are not to be

construed as absolute. It is reasonable to assume that the a crystalline form of the compound of formula I is that which is described herein if the d-values are within ± 10%, especially if within ± 5%.

Single Crystal Structure Determination

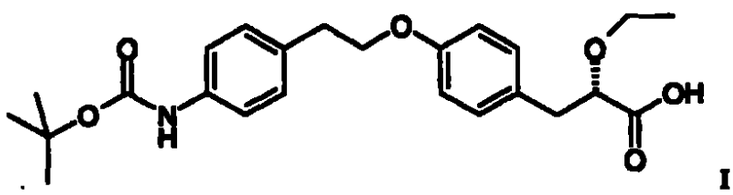
The unit cell and the crystal structure of the anhydrous form were determined from single crystal X-ray data. The unit cell was orthorhombic, with the space group $P2_12_12_1$, $Z = 4$ and the dimensions $a = 5.341$, $b = 18.757$, $c = 23.062$ Å, $\alpha = \beta = \gamma = 90°$ and $V = 2310.4$ Å^3.

Fig. 1.



Claims

1. A crystalline form of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown in formula I below



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or a pharmaceutically-acceptable salt thereof or a solvate thereof.

2. A crystalline form as claimed in claim 1 which is substantially or essentially free of solvent.

3. A crystalline form as claimed in claim 2 characterised in that it has a melting point of between 102 and 112°C.

4. A crystalline form as claimed in claim 2 characterised in that it has a X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62Å.

5. A crystalline form as claimed in claim 4 characterised in that it has a X-ray powder diffraction pattern having additional specific peaks of lower relative intensity to the first peaks at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59Å.

6. A crystalline form of a compound of formula I, as claimed in any claim from 1 to 5, for use as a medicament.

7. A pharmaceutical formulation comprising a crystalline form of a compound of formula I, as defined in any claim from 1 to 5, and a pharmaceutically acceptable

8. Use of a crystalline form of a compound of formula I, as defined in any claim from 1 to 5, in the preparation of a medicament for the treatment or prophylaxis of metabolic disease conditions, including insulin resistance syndrome.

9. The use of a substance as defined in any claim from 1 to 5 in the production of a medicament for use in treating metabolic disorders.

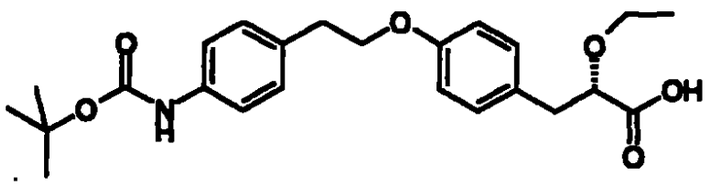
10. A method for treatment or prophylaxis of conditions associated with reduced sensitivity to insulin, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 to a patient having such reduced sensitivity to insulin.

11. A method for treatment or prophylaxis of dyslipidaemia, type II diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and/or abdominal obesity, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 to a patient in need of such treatment or prophylaxis.

12. A process for the preparation of a crystalline form of a compound of formula I which comprises crystallising the compound of formula I.

Abstract

The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as shown in formula I below



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or a pharmaceutically-acceptable salt thereof, and any solvates thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of the crystalline form of the compound, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing the crystalline form of the compound, or a solvate thereof, as active ingredient, as well as processes for the manufacture of the crystalline form of the compound, or a solvate thereof..

Astra Zeneca AB 2285-2 CO

REF: LLC-120-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

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CERTIFICACION

Se certifica que anexo se encuentra fiel copia de los documentos tal y como fueron radicados originalmente ante la Oficina de Registros y Patentes en relación con la siguiente solicitud de patente.

La solicitud se presentó originalmente en inglés.

(71) Solicitante: AstraZeneca AB, Södertälje SE

(21) Número de Solicitud de Patente. 0001422-5

(86) Fecha de presentación: 2000-04-17

Estocolmo, 2000-10-18

Por y en representación de la Oficina de Registros y patentes.

Therese Friberger (Hay firma y sello)

Derechos: 170

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

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La suscrita Anne-Marie Bonde, Notario Público de la Ciudad de Estocolmo. Suecia, certifica que THERESE FRIBERGER autorizado para firmar en nombre de la PRV, REGISTRO NACIONAL DE LA PROPIEDAD INDUSTRIAL DE SUECIA ha otorgado y firmado el documento que antecede.

Derechos: 250 Coronas

Estocolmo, 2000-10-26

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Fecha: 2000-10-30 No. 003618

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Firmado y Sellado por

MARIA SMITH RUEDA

Encargada de las Funciones Consulares

MINISTERIO DE RELACIONES EXTERIORES

No. *570403*

Fecha: Noviembre 22, 2000.

MARIA SMITH RUEDA, cuya firma aparece en el documento desempeña las funciones indicadas.

Jefe de Legalizaciones, Santafé de Bogotá D.C.

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AstraZeneca

Solicitante:	**AstraZeneca AB**
	S-151 85 Södertälje
	Suiza
Título:	**FORMA CRISTALINA**
Referencia:	H 2285-2 SE
Inventores:	BOHLIN, Martin
	BOIJE, Maria

GABRIEL RUEDA CEBRID
TRADUCTOR OFICIAL
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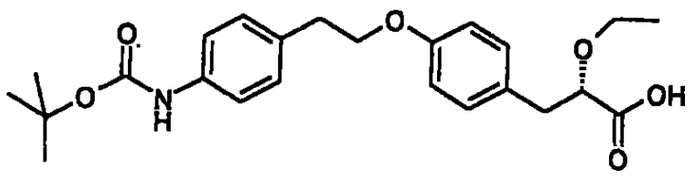
1. Una forma cristalina de la composición ácido propanoico 3-{4-[2-(4-*tert*-butoxicarbonilaminofenil)etoxi] fenil}-(S)-2-etoxi, que se aprecia en la formula I a continuación



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o una de sus sales o solvatos farmacéuticamente aceptables.

2. Una forma cristalina según se describió en la reivindicación 1 que es sustancial o esencialmente libre de solventes.

3. Una forma cristalina según se describió en la reivindicación 2 que se caracteriza por tener un punto de fusión entre 102 y 112°C.

4. Una forma cristalina según se describió en la reivindicación 2 que se caracteriza por cuanto tiene un patrón de difracción de polvos de rayos X que contiene picos específicos de alta intensidad a 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 y 3.62Å.

5. Una forma cristalina según se describió en la reivindicación 4 que se caracteriza por cuanto tiene un

patrón de difracción de polvos de rayos X con picos adicionales específicos de intensidad relativa menor con respecto de los primeros picos en los puntos 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 y 2.59A.

6. Una forma cristalina de una sal de sodio de la composición que aparece en la formula I anterior, que se caracteriza por cuanto tiene un termograma DSC que muestra un endotermo con aparición extrapolada de temperatura entre 168-178°C.

7. Una forma cristalina de una composición de la formula I, según se describió en una de las reivindicaciones de 1 a 6, para uso en terapia médica.

8. Una formulación farmacéutica que comprende una forma cristalina de una composición de la formula I, según se describió en una de las reivindicaciones 1 a 6, y uno de sus adyuvantes, diluyentes o portadores farmacéuticamente aceptables.

9. La utilización de una forma cristalina de una composición de la formula I, según se definió en una de las reivindicaciones 1 a 6, para la preparación de un medicamento para el tratamiento o profilaxis de una condición patológica del metabolismo, incluyendo el síndrome de resistencia a la insulina.

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10. El uso de una sustancia según se definió en una de las reivindicaciones de 1 a 6 para la producción de un medicamento para utilizarlo en el tratamiento de trastornos metabólicos.

11. Un método para el tratamiento o profilaxis de condiciones asociadas con reducción de la sensibilidad a la insulina, el cual comprende la administración de una cantidad terapéuticamente eficaz de una composición de acuerdo con una de las reivindicaciones 1 a 6, a un paciente que presente tal reducción de sensibilidad a la insulina.

12. Un método para el tratamiento o profilaxis de la dislipidemia, diabetes mellitus tipo 2, hiperglicemia, hiperinsulinemia, hipertensión arterial y/o obesidad abdominal, donde dicho método comprende la administración d una cantidad terapéuticamente eficaz de una composición de acuerdo con una de las reivindicaciones 1 a 6 a un paciente que necesite de dicho tratamiento o profilaxis.

13. Un proceso para la preparación de una forma cristalina de una composición de la formula I que comprende la cristalización de la composición de dicha formula I.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por **GABRIEL RUEDA CHADID (Traductor Oficial)**. Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Bogotá D.C., Noviembre 28, 2000.

GABRIEL RUEDA CHADID
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PRV

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Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

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This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* / *Applicant (s)* — *AstraZeneca AB, Södertälje SE*

(21) *Patentansökningsnummer* / *Patent application number* — *0001422-5*

(86) *Ingivningsdatum* / *Date of filing* — *2000-04-17*

Stockholm, 2000-10-18

För Patent- och registreringsverket
For the Patent- and Registration Office

Therese Friberger

Therese Friberger

Avgift
Fee 170:-

La infrascrita Anne-Marie Bonde, Notario Público de Estocolmo, Suecia, certifica que

THERESE FRIBERGER

autorizado para firmar en nombre de la PRV, REGISTRO NACIONAL DE LA PROPIEDAD INDUSTRIAL DE SUECIA ha otorgado y firmado el documento que antecede.

Derechos 250 - Estocolmo, 2000-10-26

Corono[illegible] Da oficio:

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AstraZeneca

PRJ00-04-17M

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Applicant: **AstraZeneca AB**
S-151 85 Södertälje
Sweden

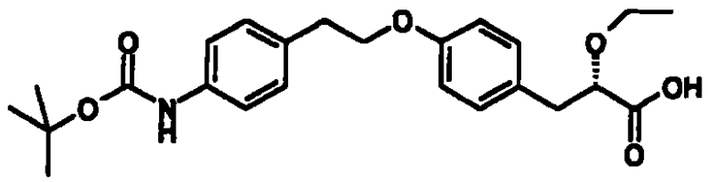
Title: **CRYSTALLINE FORM**

Reference: **H 2285-2 SE**

Inventors: **BOHLIN, Martin**
BOIJE, Maria

Crystalline Form

The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown by the formula I (set out below),



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or pharmaceutically acceptable salts thereof, and any solvates thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as active ingredient, as well as processes for the manufacture of a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance in obtaining a commercially viable manufacturing process, and also for subsequent manufacture of pharmaceutical formulations comprising the active compound.

Chemical stability, solid state stability, and shelf life of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physical

characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide drug in a form which is as chemically pure as possible.

Amorphous materials may present significant problems in this regard. For example, such materials are typically more difficult to handle and to formulate compared with crystalline forms, provide for unreliable solubility, and are often found to be unstable and chemically impure.

The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable, drug compositions, it is desirable, wherever possible, to provide drug in a substantially crystalline, and stable, form.

It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallisation behaviour of a compound will be, and this can usually only be determined empirically.

The above compound is intended for therapeutic use in Insulin Resistance Syndrome (IRS) which refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possible type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality,

notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally well-defined disease.

The present invention relates to a crystalline solid form of the compound of formula I. Significant advantages can arise when the compound of formula I can be isolated in a crystalline form, for example, in the manufacture of the compound to the purity levels and uniformity required for regulatory approval and for ease and uniformity of formulation.

We have isolated the compound of formula I as a crystalline solid that exists in a form which is substantially or essentially free of solvent (hereinafter referred to as "the anhydrous form"). Alternatively a solvated form may be formed, for example, a hydrated form. In a further alternative we have also isolated a crystalline form of the sodium salt of the compound of formula I.

We present as a feature of the invention a crystalline form of a compound of formula I, or a solvate thereof. In an alternative feature of the invention we present a crystalline form of a pharmaceutically acceptable salt of the compound of formula I, or a solvate thereof.

By the use of the term "solvated" we include the term hydrated.

By the use of the term "a crystalline form" we mean each and everyone possible crystalline form of the compound of formula I, preferably an anhydrous form.

A crystalline form of the compound of formula I can be defined by reference to its melting point, powder X-ray diffraction pattern and single crystal X-ray data

The melting point of a crystalline form of the compound of formula I generally depends on the level of purity and may be determined by conventional procedures well known in the art, for example, by differential scanning calorimetry (DSC). Typically, the anhydrous form has a melting point which is in the range 102-112°C, for example about 105-109°C.

The anhydrous has a X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62 Å. Additional specific peaks of lower relative intensity to the first peaks are at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59 Å.

A crystalline form of the compound of formula I may be obtained from a non-crystalline form of the compound of formula I, by crystallisation from a suitable solvent (including organic solvents, aqueous solutions and mixtures thereof), such as isooctane, butylacetate and toluene, or a mixture of solvents, such as a mixture of ethanol and water. To initiate crystallisation, seeding with crystalline compound of formula I may be required. Crystallisation of the compound from an appropriate solvent system may be achieved by attaining supersaturation, for example, by cooling, by solvent evaporation and/or by the addition of an anti-solvent (a solvent in which the compound of formula I is poorly soluble, examples of suitable anti-solvents include heptane and isooctane). Crystallisation temperatures and times will vary depending upon the concentration of the compound in solution, the solvent system used and the method of crystallisation adopted.

A crystalline form of the compound of formula I may be isolated using techniques well known to those skilled in the art, for example, by decanting, filtration or centrifuging. Similarly the crystalline form may be dried in accordance with well-known procedures.

Optional re-crystallisation step(s) may be performed using the same or different solvent systems to reduce further impurities, such as amorphous material, chemical impurities or to convert the crystalline into a solvated/hydrated form or an

anhydrous form.

Preferably the compound of formula I is crystallised directly from the reaction solution. Alternatively crystallisation may be performed from a subsequent solution.

A further feature of the invention is a process for the production of a crystalline form of a compound of formula I which comprises crystallising the compound of formula I.

By the use of the term "the anhydrous form", we do not exclude the presence of some solvent, including water, within the crystal lattice structure. Solvent, including water, may also be present outside the crystal lattice structure.

A feature of the invention is a crystalline form of a compound of formula I, as described above, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a crystalline form of a compound of formula I, as described above, in association with a pharmaceutically acceptable diluent or carrier. The use of a crystalline form of a compound of formula I as described above, in the preparation of a pharmaceutical composition by bringing into association a crystalline form of a compound of formula I with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above

compositions may be prepared in a conventional manner using conventional excipients.

The amount of a crystalline form of a compound of formula I, as described above, that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.001 mg to 50 mg of active agent mixed with an appropriate and convenient amount of excipient(s) which may vary from about 10 to about 99.9999 percent by weight of the total composition.

The invention also includes the use of the crystalline compound of the invention, as described above in the production of a medicament for use in:

(i) treating dyslipidaemia;

(ii) treating type 2 diabetes mellitus;

(iii) treating hyperglycaemia;

(iv) treating hyperinsulinaemia;

(v) treating hyperlipidaemia;

(vii) treating arterial hypertension; and/or

(viii) treating abdominal obesity.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal, preferably a human, requiring such treatment, an effective amount of a crystalline form of a compound of formula I, as described above.

The size of the dose for therapeutic or prophylactic purposes of a crystalline form of a compound of formula I will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine.

A crystalline form of the compound of formula I may be administered as a sole therapy or it may be administered in conjunction with other pharmacologically active agents such as an anti-diabetic, anti-hypertensive, diuretic or anti-hyperlipidaemic agent.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-50 mg/kg body weight, preferably 0.01-10 mg/kg body weight.

Crystalline forms prepared in accordance with the Example(s) below showed essentially the same powder X-ray diffraction patterns and/or DSC thermograms. It was clear when comparing the relevant patterns/thermograms (allowing for experimental error) that the same crystalline form had been formed. DSC onset temperatures may vary in the range ±5°C (for example ±2°C), and powder X-ray diffraction pattern distance values may vary in the range ±5 on the last decimal place.

Abbreviations

THF tetrahydrofuran
EtOH ethanol
i-PrOAc iso-propylacetate
EtOAc ethylacetate
DMSO dimethylsulfoxide

Synthesis 3-(4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl)-(S)-2-ethoxy propanoic acid

1) Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl) propanoate

a) Preparation of ethyl 2-ethoxyethanoate

A solution of 2-chloroacetic acid (50 g, 529 mmol, 1.0 eq) in absolute ethanol (110

ml, 2.2 vol. (where vol. Hereinafter means volume equivalent) was charged to an ethanol solution of sodium ethoxide (494 ml, 90 g, 1.32 mol, 2.5 vol.). The temperature during the charging was kept at 15-25°C. When the charging was completed the temperature was raised to 50°C. The reaction mixture was cooled to 15°C when >95% conversion was achieved. HCl (g) was then charged until the pH of the mixture was < 1. When the conversion was >95% the slurry was cooled to 15°C and neutralised to pH 5-7 with sodium ethoxide solution (approximately 5-20% of the initially charged amount). After neutralisation the slurry was cooled to 5°C and ethyl acetate (150 ml, 3 vol.) was charged. The sodium chloride formed in the reaction was then filtered off and washed with ethyl acetate. The solution was then evaporated. Maximum remaining ethanol was 20 w/w %

The overall yield of the subtitle compound was 58% of the theoretical value (loss was in evaporation). The chemical purity was >99%.

b) Preparation of ethyl 2-ethoxy-3-(4-methoxyphenyl) propenoate

4-Methoxybenzaldehyde (100 g, 734 mmol, 1.0 eq.) and ethyl 2-exthoxyethanoate (116 g, 881 mmol, 1.2 eq.) was dissolved in THF (600 ml, 6 vol.) under an atmosphere of nitrogen. The solution was cooled to –20°C. To the resulting solution, a solution of potassium *tert*-butoxide (98.8 g, 880 mmol, 1.2 eq) in THF (704 ml, 7.1 vol. corresponding to potassium *tert*-butoxide) was slowly charged while maintaining the temperature < -10°C. After the charging was completed, the reaction mixture was stirred for 1 hour at a temperature of -15°C to -10°C. To the slurry, was then charged with glacial acetic acid (53 g, 1.24 mol, 1.7 eq.) maintaining the temperature at < +5°C. The THF was then evaporated until about 1/3 remained. Toluene (824 ml, 8.24 vol.) was added and the rest of the THF evaporated. Water (200 ml, 2 vol.) and methanesulfonic acid (50 ml, 0.5 vol.) were added to the toluene slurry to give a pH in the water layer of 2-3. The water layer was separated off. The toluene layer was then evaporated to remove the remaining water. To the toluene solution was added methanesulfonic acid (2.11 g, 22 mmol, 0.03 eq). The toluene solution was refluxed with a Dean-Starke device

solution was then washed with sodium hydroxide (aq., 48%) (1.83 g, 22 mmol, 0.03 eq.) diluted in water (15 ml).

The overall yield of the subtitle compound was approximately 52% of the theoretical value.

c) Preparation of 2-ethoxy-3-(4-methoxyphenyl) propenoic acid

NaOH (aq., 48%) (122 g, 1.46 mol, 2.0 eq.), water (244 ml, 2.44 vol.) and EtOH (90 ml, 0.9 vol.) were charged to the toluene solution of ethyl 2-ethoxy-3-(4-methoxyphenyl) propenoate (approximately 96 g, 382 mmol, 0.52 eq.). The reaction mixture was heated to 50°C and stirred until full conversion was achieved. After the reaction was complete, the toluene layer was separated off and the water layer was then washed with toluene (100 ml, 1 vol.). After separation, the water layer was cooled to +5°C and acidified with conc. HCl (approximately 173 ml, 2.1 mol, 2.9 eq.). The temperature was kept < 10°C during the charging of the acid. EtOAc (100 ml, 1 vol.) was added to the acidic water slurry. After extraction the phases were separated. The EtOAc solution was evaporated and toluene (288 ml, 3 vol.) was added. The toluene solution was seeded with 2-ethoxy-3-(4-methoxyphenyl) propenoic acid and cooled to 0°C. After crystallisation the material was filtered. The wet substance was used without drying in the subsequent step.

The overall yield of the subtitle compound was 42% of the theoretical value for step b) and c) together. The chemical purity was 99.7 %.

d) Preparation of 2-ethoxy-3-(4-methoxyphenyl) propanoic acid

Palladium on charcoal (5%, 60% water wet) (13.2 g, 0.26 g Pd, 2.44 mmol Pd, 0.0054 eq.) was charged to a solution of 2-ethoxy-3-(4-methoxyphenyl) propenoic acid (100 g, 450 mmol, 1.0 eq.) in ethanol (800 ml, 8 vol.) under a nitrogen atmosphere. The vessel was then pressurised with hydrogen to 4 bar total pressure. The hydrogenation was continued until full conversion was achieved. The catalyst was filtered off and the ethanol was evaporated under vacuum. Toluene (500 ml, 5

vol.) was added and then evaporated off. The residue was dissolved in toluene (500 ml, 5 vol.) and evaporated to a volume of 260 ml. The solution was heated to 50°C and isooctane (800 ml, 8 vol.) was added. The solution was cooled to 35°C and then seeded with 2-ethoxy-3-(4-methoxyphenyl) propanoic acid. The temperature was maintained at 35°C for 30 min. The thin slurry was then cooled at a rate of 10°C/hour down to +5°C which was maintained overnight. The crystals were then filtered off and washed with isooctane (220 ml, 2.2 vol.) The crystals were dried under vacuum at 30°C.

The yield of the subtitle compound was 88% of the theoretical value. The chemical purity was 99.8 %.

e) Preparation of (1*S*)-1-(1-naphthyl)-1-ethanaminium (2*S*)-2-ethoxy-3-(4-methoxyphenyl) propanoate

A solution of 2-ethoxy-3-(4-methoxyphenyl) propionic acid (100 g, 446 mmol, 1.0 eq.) in i-PrOAc (2000 ml, 20 vol.) was stirred at 0-5°C under a nitrogen atmosphere. (S)-1-(1-naphthyl) ethylamine (45.8 g, 268 mmol, 0.6 eq.) was added to the resulting solution. The resulting suspension was heated to 75-80°C to dissolve all particles, thereby achieving a solution. The solution was then cooled and seeded with (2*S*)-2-ethoxy-3-(4-methoxyphenyl) propanoic acid (*S*)-1-(1-naphthyl) ethylamine salt. The desired diastereomeric salt was collected by filtration. The crystals were washed with i-PrOAc.

The (2*S*)-2-ethoxy-3-(4-methoxyphenyl) propanoic acid (1*S*)-1-(1-naphthyl) ethylamine salt obtained (67 g, 169 mmol, 1.0 eq.) was dissolved by heating to 75-80°C in i-PrOAc (1340 ml, 20 vol.). The product obtained was collected by filtration, washed with i-PrOAc and dried under vacuum, at 40°C, to a constant weight.

The overall yield over the two crystallisation steps was 74% of the theoretical value. The chemical purity was > 99%. The enantiomeric excess (e.e.) was 97.8%.

f) Preparation of (*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoic acid

(2*S*)-2-Ethoxy-3-(4-methoxyphenyl) propanoic acid (1*S*)-1-(1-naphthyl) ethylamine salt (100g, 253 mmol, 1.0 eq.) was suspended in toluene. The mixture was then treated with NaOH (11.1 g, 278 mmol, 1.1 eq.) in water (280 ml, 5 vol.). The upper toluene layer containing the chiral amine was separated. The lower aq. layer was washed with two more portions of toluene (280 ml, 5 vol.). The lower aq. layer was acidified to pH = 1 with aq. 37% HCl (30 g, 304 mmol, 1.2 eq.). The water solution containing (S)-2-ethoxy-3-(4-methoxyphenyl) propanoic acid was extracted with two portions of EtOAc (280 ml, 5 vol.). The combined EtOAc extract was washed with one portion of water (280 ml, 5 vol.). The solvent was replaced with NMP under reduced pressure.

NaOH (beads) (45.5 g, 1.14 mol, 4.5 eq.) and octanethiol (129 g, 154 ml, 884 mmol, 3.5 eq.) were charged to the solution of (S)-2-ethoxy-3-(4-methoxyphenyl) propanoic acid (approximately 56.6 g, 253 mmol, 1.0 eq.) in NMP (680 ml, 12 vol.) under a nitrogen atmosphere. The reaction mixture was heated to 120°C and kept at 115-125°C until the reaction was complete as determined by HPLC.

The reaction mixture was cooled to 60°C and then quenched with water. The pH was then adjusted to 2-3 with conc. HCl. The temperature was maintained at 60-70°C. Two layers were formed, the upper layer of which containing mainly octanethiol and the corresponding methyl ether (formed in the reaction). The layers were separated and the layer containing water and NMP was concentrated to 3-4 volumes under vacuum at 80-100 °C inner temperature.

The residue was extracted with a mixture of water:EtOAc. The EtOAc solution was subsequently washed 3 times with a 15% NaCl solution. The EtOAc was evaporated and the residue was directly used in the subsequent step or could also be crystallised from toluene to yield a white solid.

The yield was 51% using crystallisation, 90% using only evaporation. The chemical

purity was 99.8%. The enantiomeric excess (e.e.) was 97.8%.

g) Preparation of ethyl (*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate

(*S*)-2-Ethoxy-3-(4-hydroxyphenyl) propanoic acid (874 g, 4.16 mol, 1.0 eq.) was dissolved in EtOAc (1250 ml). To this solution were charged ethanol (3000 ml) and HCl (37%, aq.) (40 ml, 0.48 mol, 0.12 eq.). The solution was heated to boiling (about 72°C) and water/EtOAc/EtOH (2000 ml) was distilled off. Another portion of EtOH (2000 ml) was charged and another 2000 ml was distilled off. This procedure was repeated once more. At this point approximately 95% conversion was reached. Then EtOH (99.5%, 1000 ml) was added and evaporated off. This was repeated until a conversion of > 97.5% was achieved. The solution was then concentrated to a volume of 1700-2000 ml under vacuum and then cooled to 20°C.

The EtOAc solution containing ethyl *(S)*-2-ethoxy-3-(4-hydroxyphenyl) propanoate was then charged slowly (30-40 min) under vigorous stirring to a solution of $NaHCO_3$ (7% w/w, 3500 ml). Crystallisation occurred after a few minutes. After charging, the slurry was cooled to 0-5°C and then stirred at 0-5°C for at least one hour. The crystals were then filtered off and dried under vacuum.

The yield was about 93%. The chemical purity was > 99%. The enantiomeric excess (e.e.) was > 97.8 %.

<u>2) 4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester</u>

2-(4-Aminophenyl)ethanol (500 g, 3.65 mol) was charged to THF (4000 ml). The mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (796 g, 3.65 mol), was dissolved in THF (1000 ml). The THF solution of di-*tert*-butyl dicarbonate was then charged to the 2-(4-aminophenyl)ethanol in THF at 0 °C over 100 minutes. The mixture was heated to 20 °C over 3 hours and then stirred for 13 hours at 20 °C. Additional di-*tert*-butyl dicarbonate (41 g, 0.05 eq) was then added portion-wise

The residue (1450 g) was poured out on heptane under stirring. The slurry formed was filtered and the crystals washed with heptane (1000 ml). The crystals were dried under reduced pressure at 35 °C yielding 822 grams of 4-(2-hydroxyethyl)phenylcarbamic acid *tert*-butyl ester.

3) 2-[4-*tert*-Butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate

4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester (822 g, 3.46 mol) was dissolved in methylene chloride (4800 ml). Pyridine (548 g, 6.93 mol) was added and the solution cooled to 13 °C. p-Toluenesulphonyl chloride (991 g, 5.2 mol) was dissolved in methylene chloride (2400 ml). The solution containing p-toluenesulphonyl chloride was charged over one hour to the solution of 4-(2-hydroxyethyl)phenylcarbamic acid *tert*-butyl ester. The reaction was heated to 20 °C over 2.5 hours. The reaction was then kept at 20-25 °C for 18 hours. The methylene chloride solution was then washed with water (2×4000 ml) and afterwards dried with $MgSO_4$ (130 g). The salt was filtered off and the solvent evaporated. The remaining (2000 g) was poured out on heptane (5000 ml). The crystals formed were filtered off and washed with heptane (2000 ml), yielding 1600 g (wet) (drying sample gives 1320 g dry). The wet substance was then re-crystallised.

Re-crystallisation

2-[4-*tert*-Butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (wet, 3209 g) was dissolved in ethanol (6000 ml) at 55 °C. Water (600 ml) was added and the solution was cooled to 48 °C where crystallisation took place. The slurry was kept at 48 °C for 30 minutes and then cooled to 3 °C over 3 hours. The crystals were filtered and washed with cold ethanol (2×500 ml). The crystals were dried under reduced pressure at 35 °C for 25 hours, yielding 2330 g of 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate.

4) 3-[4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl]-(S)-2-ethoxypropanoic acid ethyl ester

Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (250 g, 1.05 mol, 1.0 eq) was dissolved in DMSO (500 ml). When a homogenous solution was formed, NaOH (s) beads, 20-40 mesh (48.2 g, 1.21 mol, 1.15 eq) was added followed by addition of a further 500 ml DMSO. 2-[4-*tert*-Butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (431 g, 1.10 mol, 1.05 eq) was dissolved in DMSO (1000 ml). The DMSO solution of 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate was then added over 10 minutes at 20-25 °C to the solution of ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate. The reaction mixture was then stirred for 1 hour. To fully convert ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate to ethyl 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoate an additional amount 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (20 g, 0.05 mol, 0.05 eq) and NaOH (s) beads, 20-40 mesh (2.1 g, 0.05 mol, 0.05 eq) was added. The reaction mixture was stirred for another 3 hours. The mantle was then cooled to 10°C.

5)3-{4-[2-(4-tert-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

NaOH (aq) 1M (1.15 l, 1.15 mol, 1.10 eq) was added to a solution of ethyl 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoate over 30 minutes at 19-23 °C. Stirring was continued for 1 hour, and then water (4000 ml) was added. The water layer was washed with methyl *tert*-butylether (3×2000 ml). The water layer was then acidified to pH 3 with $KHSO_4$ (aq) 1M (1.6 l, 1.6 mol, 1.5 eq). The acidic water solution was then extracted with EtOAc (3×2000 ml). The ethyl acetate parts were put together and washed with water (4×2000 ml). The ethyl acetate solution was dried with $MgSO_4$ (90 g). The salts were filtered off and washed with EtOAc (3×100 ml). The filtrate was evaporated to dryness. The oil residue (750 g) was dissolved in toluene (1750 ml). The solution was seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid and the crystallisation was continued for 30 minutes. Then isooctane (3500 ml) was added. The slurry was stirred for 15 minutes and then filtered. The solid was washed with toluene:isooctane 1:2 (400 ml) followed by water (300 ml). Drying at 40°C ...

reduced pressure yielded 382 g (0.89 mol) of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white powder.

Re-crystallisation from Butyl acetate and Isooctane

3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (382 g, 0.89 mol, 1.0 eq) was dissolved in butyl acetate (2100 ml) at 40°C. The solution was cooled to -5°C and then seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid. The crystallisation started immediately. The mixture was cooled to –15°C over 1 hour. Isooctane (2000 ml) was then added to the slurry over 50 minutes. The slurry was stirred for another 10 minutes and then filtered off. The solid was then washed with cold butyl acetate:isooctane 1:1 (1000 ml). The solid was dried using reduced pressure at 40°C, yielding 340 grams (0.79 mol) of crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white powder.

Re-crystallisation from Ethanol and H_2O

Two batches of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (680 g, 1.58 mol, 1.0 eq) were dissolved in ethanol (2100 ml) at 40°C. To the solution water (1000 ml) was added over 20 minutes at 40°C. The solution was seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (0.3 g). Water (4100 ml) was added over 70 minutes. The slurry was then cooled to 5°C over 100 minutes. The slurry was stirred for another 20 minutes and then filtered off. The solid was washed with cold ethanol:water 2:5 (1500 ml). The solid was dried using reduced pressure at 55°C, yielding 667 grams (1.55 mol) 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white solid.

Melting Point Determination

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in: Höhne, G. W. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

DSC of the anhydrous form showed an endotherm with an extrapolated onset temperature of *ca* 107 °C (*ca* 112 J/g). Thermogravimetric analysis was performed using a Mettler Toledo TGA850 instrument and showed a decrease in mass of *ca* 0.15% when the compound melts, followed by decomposition.

DSC of the anhydrous form of the sodium salt showed an endotherm with an extrapolated onset temperature of *ca* 173°C (*ca* 54 J/g). Thermogravimetric analysis was performed using a Mettler Toledo TGA850 instrument and showed a decrease in mass of *ca* 1% when the compound melts, followed by decomposition

X-ray Powder Diffraction Pattern Determination

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in: Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley and Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. and Alexander, L. E. (1974), *X-Ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD diffractometer.

The crystals of an anhydrous form were analysed by XRPD and the result is tabulated below in Table 1 (in which RI represents relative intensity), and shown in Figure 1. The diffractogram was measured with variable slits and without internal standard. The intensities are based on the intensities observed in a variable slit measurement without background subtraction. The relative intensities are less reliable, and instead of numerical values the following definitions are used:

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3 %	w (weak)

Some additional weak or very weak peaks found in the diffractogram have been omitted from Table 1.

Table 1. X-ray powder diffraction data for the anhydrous crystalline form of the compound of formula I, shown in Figure 1.

d-value/Å	RI	d-value/Å	RI
14.4	s	3.42	m
9.7	m	3.36	m
9.3	vs	3.31	m
8.6	m	3.11	m
7.2	m	3.07	s
7.1	m	3.03	m
6.0	s	3.00	m
5.7	s	2.95	m
5.5	vs	2.90	m
5.2	m	2.84	m
4.99	s	2.79	m
4.89	vs	2.77	m
4.83	vs	2.59	s
4.67	vs	2.46	m
4.53	s	2.43	m
4.46	s	2.34	m
4.33	s	2.31	m
4.28	s	2.28	m
4.22	vs	2.24	m
4.05	m	2.20	m
3.99	s	2.17	m
3.90	m	2.11	m
3.82	vs	2.08	m
3.70	s	2.00	m
3.62	vs	1.96	m
3.54	s	1.91	m
3.47	s		

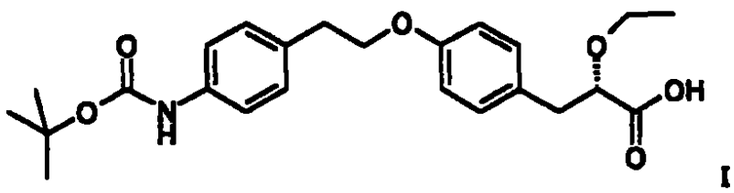
It will be understood that the d-values of the X-ray powder diffraction patterns may vary slightly from one instrument to another and so the values quoted are not to be construed as absolute. It is reasonable to assume that a crystalline form of a compound of formula I is that which is described herein if the d-values are within ± 5 on the last decimal place, especially if within ± 2 on the last decimal place.

Single Crystal Structure Determination

The unit cell and the crystal structure of the anhydrous form were determined from single crystal X-ray data. The unit cell was orthorhombic, with the space group $P2_12_12_1$, $Z = 4$ and the dimensions $a = 5.341$, $b = 18.757$, $c = 23.062$ Å, $\alpha = \beta = \gamma = 90°$ and $V = 2310.4$ Å^3.

Claims

1. A crystalline form of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown in formula I below,



I

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A crystalline form as claimed in claim 1, which is substantially or essentially free of solvent.

3. A crystalline form as claimed in claim 2 characterised in that it has a melting point of between 102 and 112°C.

4. A crystalline form as claimed in claim 2 characterised in that it has a X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62 Å.

5. A crystalline form as claimed in claim 4 characterised in that it has a X-ray powder diffraction pattern having additional specific peaks of lower relative intensity to the first peaks at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59 Å.

6. A crystalline form of a sodium salt of the compound shown in formula I above, characterised in that it has a DSC thermogram showing an endotherm with an extrapolated onset temperature between 168-178 °C.

7. A crystalline form of a compound of formula I, as claimed in any claim from 1 to 6, for use in medical therapy.

8. A pharmaceutical formulation comprising a crystalline form of a compound of formula I, as defined in any claim from 1 to 6, and a pharmaceutically acceptable adjuvant, diluent or carrier.

9. Use of a crystalline form of a compound of formula I, as defined in any claim from 1 to 6, in the preparation of a medicament for the treatment or prophylaxis of metabolic disease conditions, including insulin resistance syndrome.

10. The use of a substance as defined in any claim from 1 to 6 in the production of a medicament for use in treating metabolic disorders.

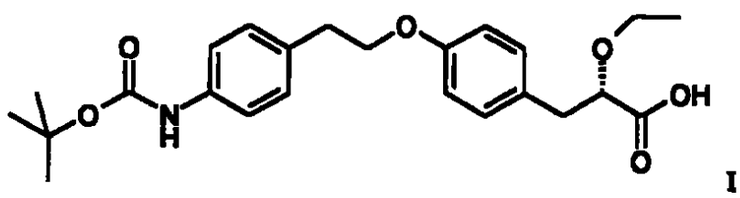
11. A method for treatment or prophylaxis of conditions associated with reduced sensitivity to insulin, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 6 to a patient having such reduced sensitivity to insulin.

12. A method for treatment or prophylaxis of dyslipidaemia, type 2 diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and/or abdominal obesity, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 6 to a patient in need of such treatment or prophylaxis.

13. A process for the preparation of a crystalline form of a compound of formula I which comprises crystallising a compound of formula I.

Abstract

The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as shown in formula I below,



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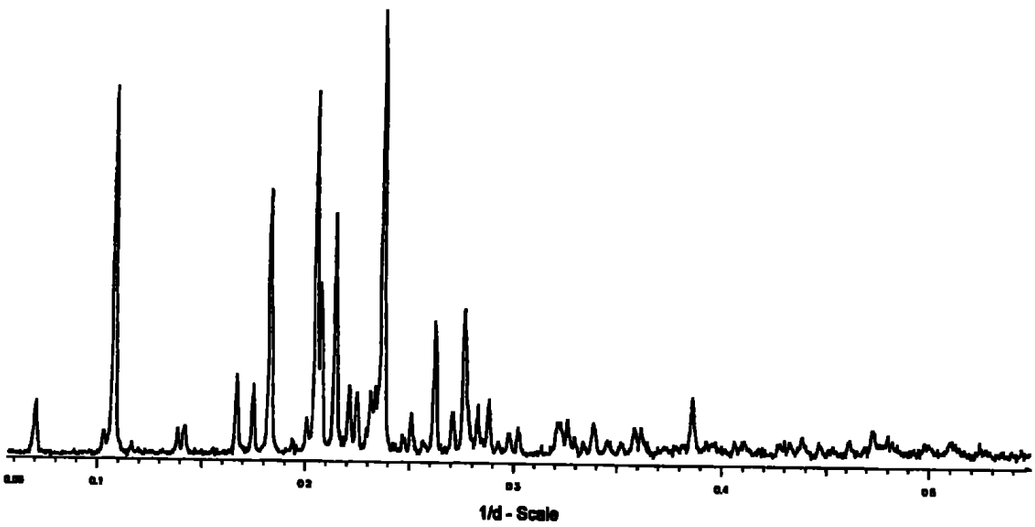
or a pharmaceutically acceptable salt thereof, and any solvates thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as active ingredient, as well as processes for the manufacture of the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

Fig. 1.



Astrazeneca
A-2285-100
88

TRADUCCION OFICIAL No. 322

LEGALIZACION DE UN DOCUMENTO PRESENTADO SIMULTANEAMENTE EN INGLES Y ESPAÑOL. TRASPASO DE LA INVENCIÓN DENOMINADA ***FORMA CRISTALINA*** *A FAVOR DE* ***ASTRAZENECA AB.***

TRASPASO

INVENCION: FORMA CRISTALINA

Firmado: **Maria Boije**

Firmado: **Martin Bohlin**

CERTIFICADO NOTARIAL (PERSONA NATURAL) SIMULTANEAMENTE EN INGLES Y EN ESPAÑOL.

Fecha: Octubre 31, 2000

Firmado: **Anne-Marie Bonde**
Notario Público

Sello: Notario Publico
Anne-Marie Bonde
Estocolmo

[illegible]

89 94

CONSULADO DE COLOMBIA
ESTOCOLMO, SUECIA

No. 003254

CERTIFICA la firma de **Anne-Marie Bonde,** como Notario Público de Estocolmo, Suecia.

Fecha: 2000-11-02

Firmado: **MARIA SMITH RUEDA**
Encargada de las Funciones Consulares

Hay sello del Consulado de Colombia en Estocolmo

MINISTERIO DE RELACIONES EXTERIORES

CERTIFICA la firma y las funciones del funcionario consular **María Smith Rueda,** bajo el número **570416,** el día Noviembre 22 del 2000.

Firmado: (Firma ilegible)
Jefe de Legalizaciones
Santafé de Bogotá, D.C.

MARIA SALOMÉ DE ARBELÁEZ
TRADUCTOR OFICIAL
RES. [illegible]

MINISTERIO DE RELACIONES EXTERIORES
394494
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2000 NOV 27 A 9 19

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

21.

JOSE LLOREDA AstraZeneca
2285-1 CO
1-5 90

ASSIGNMENT

The undersigned,

Maria Boije a Swedish citizen

domiciled in
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

Martin Bohlin a Swedish citizen

Domiciled in
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

hereby state under oath to be the sole and true inventor of

CRYSTALLINE FORM

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

domiciled in

S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

.....
Maria Boije

.....
Martin Bohlin

TRASPASO

abajo firmado

María Boije

domiciliado en
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Suecia

Martin Bohlin

AstraZeneca R&D Södertalje
S-151 85 Södertälje
Suecia

declaramos bajo juramento ser único y verdadero inventores de.

FORMA CRISTALINA

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

organizada y existente de conformidad con la leyes de Suecia

domiciliada en

S-151 85 Södertälje, Suecia.

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

.....

.....

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CERTIFICADO NOTARIAL (INDIVIDU)

A los 31 días del mes de Octubre 2000 , compareci personalmente ante mi, Notario Publico,

MARIA B O I J E y
MARTIN B O H L I N

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)
Anne-Marie Bonde

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 19 , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

93-
91

EL CÓNSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha..... 2000 - 11 - 02 ..... No: 003698
Previa la confrontación correspondiente DA
FE de que la firma que aparece en este docu-
mento es similar a la REGISTRADA aquí po:
Ayma Haidi Bonde Potanis Federico,
Estudiante Sueca

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Sede ..... dólares US$ 3
Derechos Consulares
Cuenca ..... dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

ISTERIO DE RELACIONES
EXTERIORES

570415

A FIRMA APARECE EN EL
DOCUMENTO CORRESPONDE
AS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2208 NOV 22

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA, D.C.

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, DC

Doctor
JOSE ANTONIO LLOREDA

REFERENCIA:	Radicación No.	00-91382
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	0613
	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, se le comunica que:

- Modificar el título, ya que debe definir en forma breve y precisa el objeto de la invención y estar acorde con la descripción y las reivindicaciones.

- Debe allegar el documento que acredita la representación, debidamente otorgado, a quien adelanta la actuación administrativa. Adicionalmente, deberá presentar el certificado de existencia y representación legal de la sociedad solicitante.

- Debe allegar copia del documento en que consta la cesión del derecho a la patente otorgado por el inventor al solicitante o a su causante (art. 26-k,Dec 486/2000).

En cumplimiento del artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina, se le requiere para que dentro del término de dos (2) 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 artículo 8 de la Resolución Reglamentaria No. 210 del 15 de enero del 2001.

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

El anterior requerimiento fue notificado por fijación en lista de fecha _____.

Se recuerda al interesado que debe presentar, dentro de los dieciséis meses siguientes contados a partir de la fecha de presentación de la solicitud cuya prioridad se invoca, copia de la misma certificada por la autoridad que la expidió y, en los casos en que haya lugar, la traducción simple del capítulo reivindicatorio. El incumplimiento de este plazo, acarreará la pérdida de la prioridad invocada.

202027/202022

Carrera 13 No. 27-00 Pisos 5, 7 y 10
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E-mail: info@sic.gov.co
Bogotá, D.C., Colombia