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

Re **P1 -ASTRAZENECA AB.-** Solicitud de Patente de Invención para **"FORMA CRISTALINA"** -Clase A61.-Expediente número **00-091.767** -

1 Me refiero a mi solicitud arriba nombrada de 30 de Noviembre de 2000.

2 Anexos me permito presentar a usted dos copias legalizadas, debidamente certificadas de las solicitudes de patente presentadas para el invento arriba nombrado **respecto de las cuales reclamo prioridad,** a saber·

(a) La solicitud sueca número 9904416-6 de 3 de Diciembre de 1999 debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 570398 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 483131 de 30 de Noviembre de 2000;

(a) La solicitud sueca número 0001187-4 de 3 de Abril de 2000 debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 570399 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 483130 de 30 de Noviembre de 2000, y

(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 9904416-6 y 0001187-4 de 3 de Diciembre de 1999 y 3 de Abril de 2000 respectivamente.

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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40

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

HACE CONSTAR

NOTARIO SESENTA DEL CIRCULO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CORRESPONDE CON LA FOTOCOPIA QUE HE TENIDO A LA VISTA
18 DIC 2000

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 constancia de esta certificación al interesado presenta fotocopia copia autenticada de la certificación del Ministerio de Justicia acerca de la vigencia de la resolución [illegible] 1982.

NOTARIO SESENTA DEL CIRCULO DE SANTAFE DE BOGOTA
HAGO CONSTAR
21 AGO 1998

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

Noelba Sánchez Torres
Jefe Area de Legalizaciones

01 SET 2000

NOTARIO SESENTA DEL CIRCULO DE SANTAFE DE BOGOTA
HAGO CONSTAR
01 JUL 1998

NOTARIO SESENTA DEL CIRCULO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CORRESPONDE CON LA FOTOCOPIA QUE HE TENIDO A LA VISTA
18 DIC 2000
JULIO MANUEL GUTIERREZ VARGAS
NOTARIO

NST/gcm.

República de Colombia

Ministerio de Justicia y del Derecho

41

NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
13 DIC. 2000

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 (17) del mes de noviembre de 1994.

NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
17 AGO. 1998

JUSTICIA DE COLOMBIA
SECRETARIO GENERAL

JORGE LUIS SARRIAL SARRIAL

NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
01 SET. 2000
13 DIC. 2000
NOTARIO

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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 SESENTA Y UNO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
QUE HE TENIDO A LA VISTA
13 DIC. 2000

C E R T I F I C A :

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

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 21 AGO. 1998 VIGENTE.

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

MARIA INES RODRIGUEZ TORRES
SECRETARIA

COMO NOTARIO SESENTA Y UNO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
QUE HE TENIDO A LA VISTA
08 SET. 1998

COMO NOTARIO SESENTA Y UNO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
QUE HE TENIDO A LA VISTA
01 JUL 1998
09 ENE. 1999
NOTARIO

COMO NOTARIO SESENTA Y UNO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
QUE HE TENIDO A LA VISTA
12 ENE. 2000
NOTARIO

Crm./

AstraZeneca 43
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Astra Zeneca AB 2284-TCO

REF: LLC-118-2000. 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. 9804418-6
(86) Fecha de presentación: 1998-12-03

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 5496 DE NOV. 29-93
MINISTERIO DE JUSTICIA

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. 003818

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. 570388

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 CHARRY
TRADUCTOR OFICIAL
RESOLUCION 996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

MINISTERIO DE RELACIONES EXTERIORES

183131

CUYA FIRMA APARECE EN EL DOCUMENTO ADJUNTO ES LA DE LAS FUNCIONES INDICADAS

NOV 30 14:10:20

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

Solicitante: Astra Aktiebolag
S-151 85 Södertälje
Suiza

Título: FORMA CRISTALINA

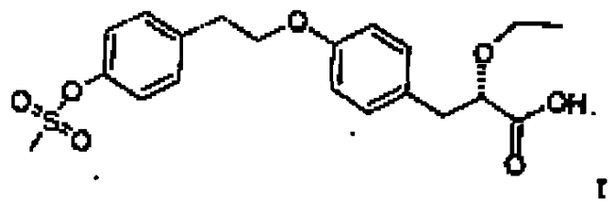
Referencia: H 2284-1

Inventores: Maria Boije

GABRIEL RUEDA CRADO
TRADUCTOR OPICIAL
RESOLUCION 1996 DE NOV. 29-02
MINISTERIO DE JUSTICIA

REIVINDICACIONES PRV 99-12-03

1. Una forma cristalina de la composición ácido propanoico (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil} etoxi)fenil]. 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 84 y 90°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 8.2, 4.47, y 4.15Å.

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

GABRIEL RUEDA CUARTO
TRADUCTOR OFICIAL
RESOLUCION 5966 DE NOV. 29-91
MINISTERIO DE JUSTICIA

respecto de los primeros picos en los puntos 4.69, 2.74, 2.72, y 2.60Å.

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 definió 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 condiciones asociadas con un paciente que presente reducción a la sensibilidad 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. 29-83
MINISTERIO DE JUSTICIA

AstraZeneca
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PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

PATENT- OCH REGISTRERINGSVERKET • PATENT- AND REGISTRATION OFFICE

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* *9904416-6*
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 150:- Estocolmo, 2000-10-26
Coronas De oficio:

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EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha 2000 -10- 30 No. 003618

Previa la confrontación correspondiente DA
FE de que la firma que aparece en este docu
mento es similar a la REGISTRADA aquí po.
Anna Maria Rueda, Notario Publico
Estocolmo, Suecia

MARIA SVATH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Siete dólares US$ 7
Derechos Consulares
Quince dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2000 NOV 22

JEFE DE LA SECCIÓN
SANITARIA INTERNACIONAL

MINISTERIO DE RELACIONES
EXTERIORES

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PRV99-ASTRA

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Applicant: Astra Aktiebolag
S-151 85 Södertälje
Sweden

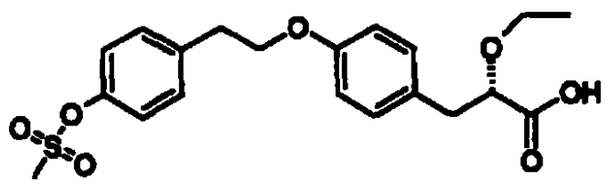
Title: **CRYSTALLINE FORM**

Reference: H 2284-1

Inventors: Maria Boije

Crystalline Form

The present invention relates to a crystalline form of the compound (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl] propanoic acid as shown in formula I below



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or a pharmaceutically-acceptable salt thereof, and solvates thereof. The invention also concerns methods of treating one or more disease conditions 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 use in one or more of said conditions. 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, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of 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 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 difficult to handle and to formulate than crystalline material, 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 useful in the treatment of metabolic diseases, such as Insulin Resistance Syndrome (IRS), defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, with fat and liver prevailing in many individuals with or without diabetes mellitus. IRS refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly 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.

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. It is therefore highly desirable to find a novel crystalline form of the compound.

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.

By the use of the term "solvated" we also include 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 84-90°C, for example about 86-88°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 comprising specific peaks of high

intensity at 6.2, 4.47 and 4.15Å. Additional specific peaks of lower relative intensity to the first peaks are at 4.69, 2.74, 2.72 and 2.60Å

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 toluene and ethyl acetate, or a mixture of solvents, such as a mixture of ethanol/water, isopropanol/water or toluene/isooctane. 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 or 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 form for 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.

Preferably the crystallisation is carried out directly from the reaction solution. Alternatively the crystallisation is 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.

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, per compound 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, 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 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 0.01 mg to 50mg of active agent mixed 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 dyslipidaemia;

(ii) treating non-insulin dependant diabetes mellitus;

(iii) treating hyperglycaemia;

(iv) treating hyperinsulinaemia;

(v) treating hyperlipidaemia;

(vi) treating arterial hypertension; and/or

(vii) 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 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 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 ±2 on the last decimal place.

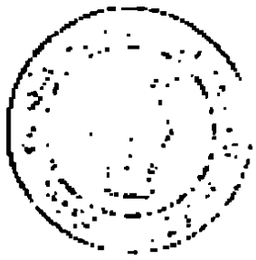
Synthesis of (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl propanoic acid

1-(Methylsulfonyloxy)-2-[4-(methylsulfonyloxy)phenyl]ethane

2-(4-Hydroxyphenyl)ethanol (356 g, 2.58 mol, 1.0 eq) was dissolved in methylene chloride (3500 ml) and triethyl amine (653 g, 6.44 mol, 2.5 eq). The mixture was cooled to -20°C. Methanesulfonyl chloride (657 g, 5.74 mol, 2.2 eq) was then added keeping the temperature between -25°C and -15°C. When the conversion was >95% salts were formed which were filtered off and washed with methylene chloride (600 ml). The organic layer was washed first with saturated sodium hydrogencarbonate solution (700 ml) at 20°C followed by water (700 ml). The methylene chloride was evaporated to dryness and the remaining was then used in the subsequent step.

Ethyl (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl propanoate

Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (325 g, 1.36 mol, 1.0 eq) was dissolved in acetonitrile (2600 ml). When a homogenous solution was formed, potassium carbonate (560 g, 4.05 mol, 3.0 eq) and magnesium sulfate (110 g, (0.2 g/g K_2CO_3)) was added. To the acetonitrile solution 1-(methylsulfonyloxy)-2-[4-(methylsulfonyloxy)phenyl] ethane (ca: 2050 ml (0.3 g/ml, 2.21 mol, 1.65 eq)) was charged and the mixture allowed to react at reflux, 82°C for 24 hours with vigorous stirring. When a conversion >98% was reached the reaction was cooled to room temperature. The remaining salts were filtered of and washed with acetonitrile



(800 ml). The filtrate was evaporated to dryness. The oil residue was then used in the subsequent step.

(S)-2-Ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl propanoic acid

To the oil of ethyl (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoate(723 g (71.2% assay), 1.18 mol, 1.0 eq) was added tetrahydrofuran (THF) (3900 ml). When a homogenous solution was formed, water (900 ml) was added. The mixture was cooled to +10°C. Lithium hydroxide solution (390 ml, 4 M, 1.45 eq) was added over 1 hour. The temperature was then raised to +30°C and the reaction allowed to proceed at this temperature for 2-3 hours. The reaction was stopped when the conversion was >99%. Ethyl acetate (500 ml) was added and the mixture cooled to room temperature. The solution was stirred for about 30 minutes and the THF was evaporated off. When about 80-90% of the THF was evaporated water (1900 ml) was added. The evaporation was continued until no THF remained in the mixture. The alkali water solution was then washed with ethyl acetate (1000 ml, 2 × 1250 ml, and 950 ml). The pH of the water solution of (S)-2-ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid was then adjusted to 2.0-2.5 with HCl (aq) (550 ml, 3.0 M). Ethyl acetate (2500 ml) was added and the phases separated. The ethyl acetate solution of (S)-2-ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid was then washed with water (700 ml) and after separation evaporated to dryness. The remaining oil was then used in the following crystallisation

Crystallisation of (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoic acid

The oil from 3 batches of (S)-2-Ethoxy-3-[4-[[4-(methylsulphonyloxy) phenethyl]oxy]phenyl] propanoic acid (1262g, 3.09 mol, 1.0 eq) was dissolved in toluene (2500 ml) at 50°C. When a clear solution was achieved the solution was evaporated to decrease the amount of ethyl acetate present. The volume before evaporation was 6750 ml. Another portion of toluene (2500 ml) was added, volume after addition 7750 ml and evaporation was continued. A third portion of toluene was then added to the solution, the volume before the addition was 6300 ml, the volume after the addition was 8800 ml. The

evaporation was continued until an opaque solution was formed, volume 8200 ml. Isooctane (1000 ml) was added to the solution which had been heated to 40°C. The crystallisation was initiated by seeding at 40°C. The mixture was vigorously stirred until a slurry was formed. The agitation rate was then decreased. The slurry was left crystallising over night. The slurry was then filtered and washed with toluene: isooctane 5:1 (1800ml). The crystals were then dried under reduced pressure at 40°C.

Recrystallisation of (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl propanoic acid

(S)-2-Ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid (1040 g (96.4% assay), 2.45 mol, 1.0 eq) was dissolved in toluene (7000 ml) at a temperature of 60°C. When a clear solution was achieved isooctane (1720 ml) was added to the solution. The solution was then filtered through Silica 60 gel. The solution was then cooled from 50°C to 45°C, at this temperature crystallisation occurred. The slurry was cooled to 20°C. The solid was then filtered and washed with toluene: isooctane (1250 ml:250 ml). The crystals were dried under reduced pressure at 40°C.

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* 87°C (*ca* 102 J/g).

Powder X-ray Diffraction Pattern Determination

The X-ray powder diffraction (XRPD) spectra were determined using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD X-ray diffractometer. 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 powder diffraction spectra of a typical sample of an anhydrous crystalline form of a compound of formula I is shown in Figure 1.

The crystals of the anhydrous form were analysed by XRPD and the results 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 the 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 form of the crystalline form of the compound of formula I is shown in Figure 1.

d-value/Å	RI	d-value/Å	RI	d-value/Å	RI
12.3	w	3.64	s	2.74	w
9.4	m	3.60	s	2.72	m
7.2	m	3.56	m	2.67	w
6.9	m	3.45	s	2.60	w

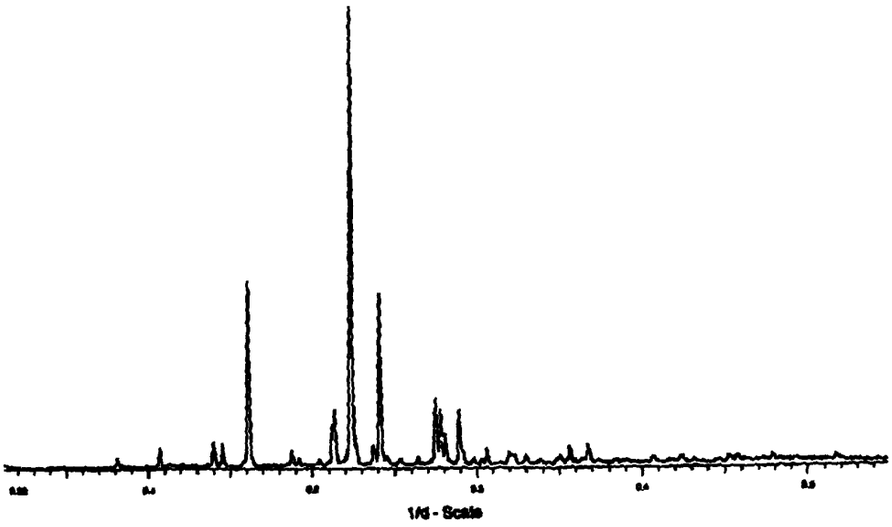
6.2	vs	3.43	m	2.45	w
5.3	m	3.35	w	2.35	w
5.2	w	3.29	w	2.31	w
4.90	w	3.26	m	2.20	w
4.69	s	3.17	w	2.18	w
4.47	vs	3.12	m	2.11	w
4.42	m	3.10	w	2.08	w
4.22	m	3.03	w	2.02	w
4.15	vs	2.95	w	1.99	w
4.08	w	2.85	w	1.93	w
3.95	w	2.80	m		
3.79	w	2.78	w		

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 X-Ray Diffraction Pattern Determination

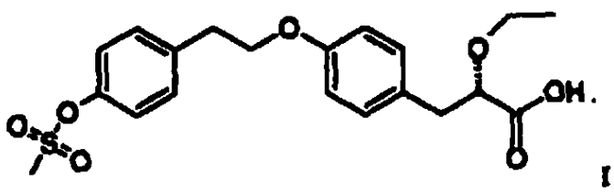
A unit cell was determined from single crystal X-ray data of the anhydrous form. It was orthorhombic with $P2_12_12_1$ symmetry, $Z = 4$, and the following dimensions: $a = 5.762$ Å, $b = 14.426$ Å, $c = 24.785$ Å, $\alpha = \beta = \gamma = 90°$ and $V = 2060.2$ Å^3.

Fig.1



Claims

1. A crystalline form of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] 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 84 and 90°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 6.2, 4.47 and 4.15Å.

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 4.69, 2.74, 2.72 and 2.60Å.

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 adjuvant, diluent or carrier.

8. Use of a crystalline form of a compound of formula I, as defined in any claim form 1 to 5 , in the preparation of a medicament for the treatment or prophylaxis of conditions associated with a patient having reduced sensitivity to insulin.

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.

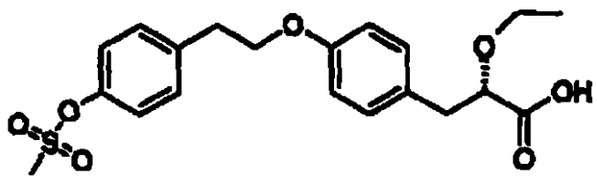
10. A method for treatment or prophylaxis of conditions associated with reduced sensitivity to insulin, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 to a patient having such reduced sensitivity to insulin.

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 a novel crystalline form of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid, shown by the formula I (set out below)



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or a pharmaceutically-acceptable salt thereof, and solvates thereof. The invention also concerns methods of treating one or more disease conditions 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 use in one or more of said conditions. 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..

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Astra Zeneca AB 2284-2 CO

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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. 0001187-4
(66) Fecha de presentación: 2000-04-03

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
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RESOLUCION 3196 DE NOV. 29-82
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La suscrita Anne-Marie Bonde, Notario Pùblico 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

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MARIA SMITH RUEDA

Encargada de las Funciones Consulares

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No. 570399

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 CUADRO
TRADUCTOR OFICIAL
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SANTAFE DE BOGOTA D.C.

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PVR00-04-03

AstraZeneca

Solicitante:	**AstraZeneca AB**
	S-151 85 Södertälje
	Suiza
Título:	**FORMA CRISTALINA**
Referencia:	H 2284-2 SE
Inventores:	BOIJE, Maria
	INGHARDT, Tord
	HORWATH, Karol

GABRIEL RUEDA CHARID
TRADUCTOR OFICIAL
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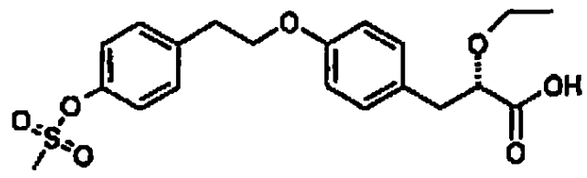
REIVINDICACIONES PRV 00-01-03

1. Una forma cristalina de la composición ácido propanoico (S)-2-etoxi-3-[4-(2-(4-metanosulfoniloxifenil) etoxi)fenil], 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 82 y 92°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 6.2, 4.47, y 4.15Å.

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

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respecto de los primeros picos en los puntos 4.69, 3.64, 3.60, y 3.45Å.

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 definió 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 condiciones asociadas con un paciente que presente reducción a la sensibilidad 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 2, 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.

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Bogotá D.C., Noviembre 28, 2000.

GABRIEL RUEDA CHADID
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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* *0001187-4*
Patent application number

(86) *Ingivningsdatum* *2000-04-03*
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 Bondo, Notario Público de Estocolmo, Suecia, certifico 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.

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EL CONSULADO DE COLOMBIA EN
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Fecha........2000 -10- 30........ No: 003617

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Anna-Maria Bjunder, Vicedirectora Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

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AstraZeneca

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

Title: **CRYSTALLINE FORM**

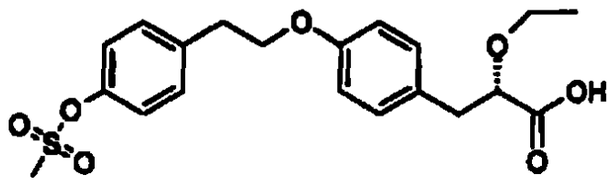
Reference: **H 2284-2 SE**

Inventors: **BOIJE, Maria**
INGHARDT, Tord
HORWATH, Karol

3 April 2000

Crystalline Form

The present invention relates to a crystalline form (or should one write: relates to crystalline form of) of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid as shown in formula I below



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or a pharmaceutically-acceptable salt thereof, and solvates thereof. The invention also concerns methods of treating one or more metabolic disease conditions, 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 of said 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, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of 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 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 than crystalline material, 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 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 suffering patients 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. The particular crystalline form isolated 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 produced, for example, a hydrated form.

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 also include 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 the crystalline form of the compound of formula I generally dependson 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 82-92°C, for example about 85-89°C.

The anhydrous form has an X-ray powder diffraction pattern containing specific peaks of high intensity at 6.2, 4.47 and 4.15 Å. Additional specific peaks of lower relative intensity to the first peaks are at 4.69, 3.64, 3.60 and 3.45 Å.

A crystalline form of a compound of formula I may be obtained from a non-crystalline form of a compound of formula I, by crystallisation from a suitable solvent (including organic solvents, aqueous solutions and mixtures thereof), such as toluene and ethyl acetate, or a mixture of solvents, such as a mixture of ethanol/water, isopropanol/water or toluene/isooctane. 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 or isooctane). Crystallisation temperatures and times will vary depending upon the concentration of the compound of formula I 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 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 form into a solvated/hydrated form or an anhydrous form.

Preferably crystallisation is carried out directly from the reaction solution.
Alternativelycrystallisation is 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 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 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 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;

(vi) treating arterial hypertension; and/or

(vii) 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 humans, 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.

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.

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 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 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

EtOAc = ethyl acetate
HPLC = high-pressure liquid chromatography
i-PrOAc = isopropyl acetate
NMP = N-methyl-2-pyrrolidinone
THF = tetrahydrofuran

Synthesis of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]-ethoxy)phenyl] 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 neutralized to pH 5-7 with sodium ethoxide solution (approximately 5-20% of the initially charged amount). After neutralization 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 >95%.

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

4-Methoxybenzaldehyde (100 g, 734 mmol, 1.0 eq.) and ethyl 2-ethoxyethanoate (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 connected until full conversion was achieved. The solution was cooled to 25°C. The 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 crystallization 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 pressurized 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 (2S)-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 (2S)-2-ethoxy-3-(4-methoxyphenyl) propanoic acid (1S)-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 crystallization 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

(2S)-2-Ethoxy-3-(4-methoxyphenyl) propanoic acid (1S)-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 H_2O: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 crystallized from toluene to yield a white solid.

The yield was 52% 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). Crystallization occured 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 %.

2) 2-(4-(Methanesulfonyloxyphenyl)ethylmethanesulfonate

2-(4-Hydroxyphenyl)ethanol (356 g, 2.58 mol, 1.0 eq) was dissolved in methylene chloride (3500 ml) and triethyl amine (653 g, 6.44 mol, 2.5 eq). The mixture was cooled to -20°C. Methanesulfonyl chloride (657 g, 5.74 mol, 2.2 eq) was then added keeping the temperature between -25°C and -15°C. When the conversion was >95%, the salt formed during the reaction was filtered off and washed with methylene chloride (600 ml). The organic layer was washed first with saturated sodium hydrogencarbonate solution (700 ml) at 20°C followed by water (700 ml). The methylene chloride was evaporated and replaced by acetonitrile. The acetonitrile solution was then used in the subsequent step.

3) Ethyl (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl]propanoate

Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl) propanoate(325 g, 1.34 mol, 1.0 eq) was dissolved in acetonitrile (2600 ml). When a homogenous solution was formed, potassium carbonate (560 g, 4.05 mol, 3.0 eq) and magnesium sulfate (110 g, (0.2 g/g K_2CO_3)) was added. The acetonitrile solution of 2-(4-(methanesulfonyloxyphenyl)ethylmethanesulfonate (total volume ca: 2050 ml (0.3 g/ml, 2.21 mol, 1.65 eq)) was charged to the reaction vessel and the mixture allowed to react at reflux, 82°C for 24 hours with vigorous stirring, keeping the volume constant by portion-wise addition of acetonitrile. When a conversion >98% was reached the reaction was cooled to room temperature. The remaining salts were filtered off and washed with acetonitrile (800 ml). The filtrate was evaporated to dryness. The residue was then used in the subsequent step.

4) (S)-2-Ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl] propanoic acid

To the oil of ethyl (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl] ethoxy)phenyl]propanoate (723 g (71.2% assay), 1.18 mol, 1.0 eq) was added THF (3900 ml). When a homogeneous solution was formed, water (900 ml) was added. The mixture was cooled to +10°C. Lithium hydroxide solution (390 ml, 4 M, 1.32 eq) was added over 1 hour. The temperature was then raised to +30°C and the reaction allowed to proceed at this temperature for 2-3 hours. The reaction was stopped when the conversion was >99%. EtOAc (500 ml) was added and the mixture cooled to room temperature. The solution was stirred for about 30 minutes and the THF was evaporated off. When about 80-90% of the THF was evaporated, water (1900 ml) was added. The evaporation was continued until no THF remained in the mixture. The alkaline water solution was then washed with EtOAc (1000 ml, 2 x 1250 ml, and 950 ml). The pH of the water solution of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]-ethoxy)phenyl] propanoic acid was then adjusted to 2.0-2.5 with HCl (aq) (550 ml, 3.0 M). EtOAc (2500 ml) was added and the phases separated. The ethyl acetate solution of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]-ethoxy)phenyl] propanoic acid was then washed with water (700 ml) and after separation evaporated to dryness. The remaining oil was then used in the following crystallisation.

Crystallisation of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl] propanoic acid

The crude material from 3 batches of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]-ethoxy)phenyl] propanoic acid (1871 g total weight, 1262 g compound, 3.09 mol, 1.0 eq) containing EtOAc (500 ml) was dissolved in toluene (5000 ml) at 50°C. When a clear solution was achieved the solution was evaporated to decrease the amount of EtOAc present. . The volume before evaporation was 6750 ml. Another portion of toluene (2500 ml) was added, volume after addition was 7750 ml, and evaporation was continued. A third portion of toluene (2500 ml) was then added to the solution, the volume before the addition was 6300 ml, the volume after the addition was 8800 ml. The evaporation was continued until an opaque solution was formed, volume 8200 ml. Isooctane (1000 ml) was added to the solution which had been heated to 40°C. The crystallisation was initiated by

seeding at 40°C. The mixture was vigorously stirred until a slurry was formed. The agitation rate was then decreased. The slurry was left crystallising over night. The slurry was then filtered and washed with toluene:isooctane 5:1 (1800 ml). The crystals were then dried under reduced pressure at 40°C.

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Recrystallisation of (S)-2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl] propanoic acid

(S)-2-Ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl] propanoic acid (1040 g (96.4% assay), 2.45 mol, 1.0 eq) was dissolved in toluene (7000 ml) at a temperature of 60°C. When a clear solution was achieved isooctane (1720 ml) was added to the solution. The solution was then filtered through Silica 60 gel. The solution was then cooled from 50°C to 45°C, at this temperature crystallisation occurred. The slurry was cooled to 20°C. The solid was then filtered and washed with toluene:isooctane 5:1(1500 ml). The crystals were dried under reduced pressure at 40°C.

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* 87°C (*ca* 102 J/g).

X-ray Powder Diffraction Pattern Determination

The X-ray powder diffractograms (XRPD) were determined using a Siemens D5000 X-ray diffractometer and/or a Philips X'Pert MPD X-ray diffractometer. 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 powder diffractograms of a typical sample of an anhydrous crystalline form of a compound of formula I is shown in Figure 1.

The crystals of an anhydrous form were analysed by XRPD and the results 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 an anhydrous form of a crystalline form of a compound of formula I, shown in Figure 1.

d-value/Å	RI	d-value/Å	RI	d-value/Å	RI
12.3	w	3.64	s	2.74	w
9.4	m	3.60	s	2.72	m
7.2	m	3.56	m	2.67	w
6.9	m	3.45	s	2.60	w
6.2	vs	3.43	m	2.45	w
5.3	m	3.35	w	2.35	w
5.2	w	3.29	w	2.31	w
4.90	w	3.26	m	2.20	w
4.69	s	3.17	w	2.18	w
4.47	vs	3.12	m	2.11	w
4.42	m	3.10	w	2.08	w
4.22	m	3.03	w	2.02	w
4.15	vs	2.95	w	1.99	w
4.08	w	2.85	w	1.93	w
3.95	w	2.80	m		
3.79	w	2.78	w		

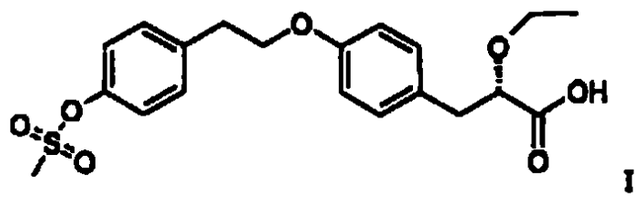
It will be understood that the d-values of the X-ray powder diffraction patterns may vary slightly from one instrument to another and so the values quoted are not to be construed as absolute. It is reasonable to assume that a crystalline form of a compound of formula I is that which is described herein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

Single Crystal X-Ray Diffraction Pattern Determination

A unit cell was determined from single crystal X-ray data of the anhydrous form. It was orthorhombic with $P2_12_12_1$ symmetry, $Z = 4$, and the following dimensions: $a = 5.762$ Å, $b = 14.426$ Å, $c = 24.785$ Å, $\alpha = \beta = \gamma = 90°$ and $V = 2060.2$ Å^3.

Claims

1. A crystalline form of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] 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 82 and 92°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 6.2, 4.47 and 4.15 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 4.69, 3.64, 3.60 and 3.45 Å.

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 adjuvant, diluent or carrier.

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 conditions associated with a patient having reduced sensitivity to insulin.

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 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 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 a compound of formula I.

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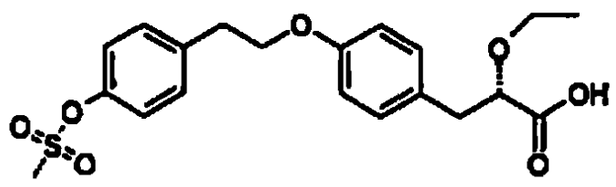
Abstract

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



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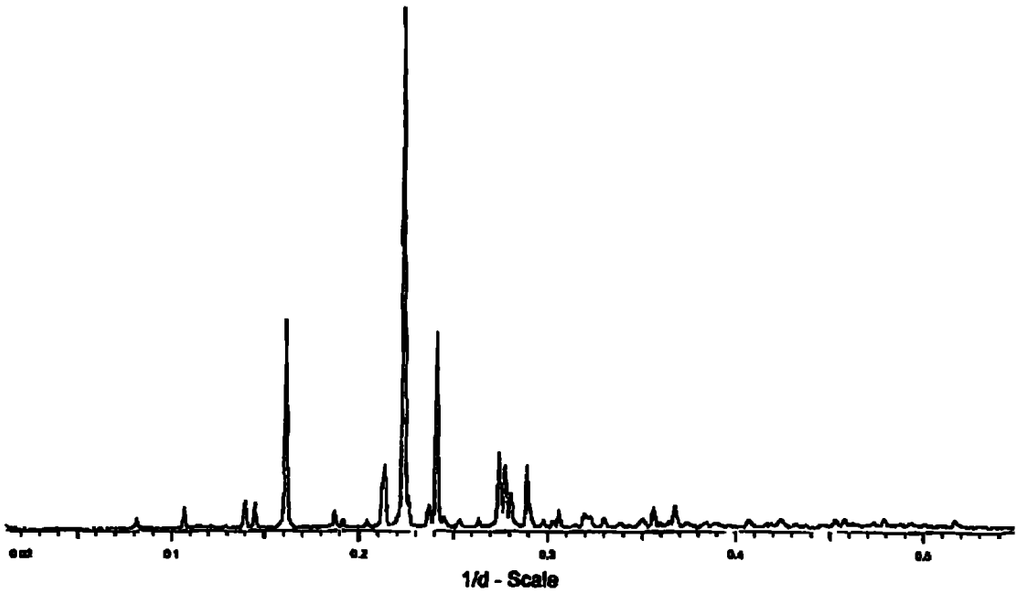
or a pharmaceutically-acceptable salt thereof, and solvates thereof. The invention also concerns methods of treating one or more metabolic disease conditions, particularly those associated with Insulin Resistance Syndrome, and the use of a crystalline form of the compound, or a pharmaceutically-acceptable salt thereof, or a solvate thereof, in the manufacture of a medicament for use in one or more of said conditions. 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.

Fig.1



Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.

Doctor
JOSE ANTONIO LLOREDA

REFERENCIA:	Radicación No.	00-91767
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	0644
	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 15 FEB. 2001

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 éste plazo, acarreará la pérdida de la prioridad invocada. .

202027/202022

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