

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00048529 0000001 Folios: 52
Fecha (Act): 2000-06-22 15:42:32
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. S D.

Re: P1.-ASTRAZENECA AB .- Solicitud de Patente de Invención para
"NUEVAS FORMAS CRISTALINAS".-Clase A61.-Expediente
número 00-048.529.-

1. Me refiero a mi solicitud de patente de fecha 28 de Junio de 2000.
2. Anexos me permito presentar a usted:
 - (1) Copia autentica, debidamente legalizada hasta por El Ministerio de Relaciones de Colombia bajo el número 087641 de 29 de Junio de 2000, de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud sueca número 9902550-4 de 2 de Julio de 1999, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento;
 - (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 la legalizaciones de la solicitud sueca número 9902550-4 de 2 de Julio de 1999.
 - (3) Documentos que acreditan el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizados hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 195048 de 6 de Julio de 2000.
 - (4) Traducción Oficial No. 180, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 093572 de 11 de Julio de 2000, correspondiente a las partes pertinentes de dicho documento de traspaso.

51 52

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

Señor Superintendente,

A handwritten signature in black ink, consisting of several overlapping loops and a long horizontal stroke extending to the right.

JOSE ANTONIO FLOREDA
T.P. 10.784
Código 231

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

HACE CONSTAR

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

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

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

Nelson Sánchez Torres
Jefe Área de Legalizaciones

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 SET 1998

PABLO MENDEZ GARCIA

NST/gtm.

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
20 ABR 1999
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
08 MAR 1999
JUAN MANUEL BOTERO MEDINA
NOTARIO

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
21 AGO 1998

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
05 ENE 1999
JUAN MANUEL BOTERO MEDINA
NOTARIO

01 JUL 1998

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

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida
cencia 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
mes de noviembre de 1994.

JORGE LUIS SABIDO AL SABIDO

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 20 ABR 1999
JUAN MANUEL BOTERO MEDINA
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JUAN MANUEL BOTERO MEDINA
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SANTAFE DE BOGOTA 21 AGO 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

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SANTAFE DE BOGOTA
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SANTAFE DE BOGOTA 23 NOV 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 06 ENE 1999
JUAN MANUEL BOTERO MEDINA
NOTARIO

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 JUL 1998
PAOLO MENUEZ BARAJAS
NOTARIO

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 23 SET 1998
PAOLO MENUEZ BARAJAS
NOTARIO

COMO NOTARIO SE LE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 20 ABR 1999
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.

08 MAR. 1999

MANUEL BOTTA
NOT.

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 INGLÉS-ESPAÑOL, ESPAÑOL-INGLÉS, en virtud de la Resolución No. 5996, se encuentra VIGENTE.

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA QUE ME TIENGO A LA VISTA
COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE ME TIENGO A LA VISTA
SANTAFE DE BOGOTA

01 JUL 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

PASLO MENDEZ COMAR, NOTARIO SEXTO DE
SANTAFE DE BOGOTA

HAGO CONSTAR
QUE LA FOTOCOPIA QUE ME TIENGO A LA VISTA
COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE ME TIENGO A LA VISTA
SANTAFE DE BOGOTA

23 NOV. 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

~~SECRETARIA~~

COMO NOTARIO DE FIDELICARADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTENTICA QUE ME TENIDO A LA VISTA
SANTAFE DE BOGOTA 08 SET 1998

CRM./

REF: LLC-064-2000. 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: Astra AB, Södertälje SE

(21) Número de Solicitud de Patente. 9902550-4

(86) Fecha de presentación: 1999-07-02

Estocolmo, 2000-05-25

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

Emma Hogberg (hay firma y sello)

Derechos: 170

REIVINDICACIONES

PRV99-07-02

1. Una forma sustancialmente cristalina del melagatran.

2. Una forma estable de melagatran.

3. Melagatran en forma que presente alta estabilidad.

4. Un compuesto según se reivindicó en una de las reivindicaciones 1 a 3, que se presenta en forma de hidrato.

5. Un compuesto según se reivindicó en una de las reivindicaciones 1 a 3, que contiene por lo menos 0.5 mol de agua por mol de melagatran.

6. Un compuesto según se reivindicó en las reivindicaciones 4 o 5, caracterizado por una curva diferencial de escaneo calorimétrico, a una velocidad promedio de calentamiento de 10°C/min en un tazón cerrado con orificio en la parte inferior del fluido de nitrógeno, mostrando un endótermo con aparición extrapolada de temperatura de aproximadamente 83°C y un calentamiento asociado de aproximadamente -125 J/gram; con patrón de difracción de polvo de rayos X caracterizado por picos cristalinos con valores "d" en 21.1, 10.5, 7.6, 7.0, 6.7, 6.4, 6.2, 5.7, 5.4, 5.3, 5.22, 5.19, 5.19, 5.07, 4.90, 4.75, 4.68, 4.35, 4.19, 4.00, 3.94, 3.85, 3.81, 3.73, 3.70, 3.63,


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia

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3.52, 3.39, 3.27, 3.23, 3.12, 3.09, 3.06, 2.75, 2.38 y 2.35Å;
y/o un contenido hídrico de 4.3% (w/w).

7. Un compuesto según se reivindicó en una de las reivindicaciones 1 a 3, que se presenta en forma de anhidrato.

8. Un compuesto según se reivindicó en la reivindicación 7 caracterizado por un patrón de difracción de polvo de rayos X caracterizado por picos cristalinos con valores "d" en 15.9, 15.1, 10.9, 8.9, 8.4, 8.0, 7.0, 6.8, 6.4, 6.2, 6.0, 5.8, 5.5, 5.3, 5.0, 4.87, 4.81, 4.71, 4.61, 4.45, 4.08, 3.97, 3.82, 3.76, 3.66, 3.44, 3.32 y 3.20Å.

9. Un compuesto según se reivindicó en la reivindicación 7 caracterizado por una curva diferencial de escaneo calorimétrico, a una velocidad promedio de calentamiento de 10°C/min. en un tazón cerrado con orificio debajo del fluido de nitrógeno, que muestra un endótermo con temperatura extrapolada de aparición de aproximadamente 210°C y calor asociado de aproximadamente -120 J/g; y/o un patrón de difracción de polvo de rayos X caracterizado por picos cristalinos con valores "d" en 17.8, 8.9, 8.1, 7.5, 6.9, 6.3, 5.9, 5.6, 5.5, 5.4, 5.3, 5.2, 5.0, 4.71, 4.43, 4.38, 4.33, 4.14, 4.12, 4.05, 3.91, 3.73, 3.61, 3.58, 3.56, 3.47, 3.40, 3.36, 3.28, 3.24, 3.17, 3.09, 3.01, 2.96, 2.83, 2.54, 2.49, 2.41, 2.38 y 2.35Å.

10. Un compuesto según se reivindicó en una de las reivindicaciones 1 a 3, que se presenta en forma de isopropanolato/hidrato mezclado.

11. Un compuesto según se reivindicó en la reivindicación 10, caracterizado por un patrón de difracción de polvos de rayos X caracterizado por picos cristalinos con valores "d" en 19.7, 13.1, 11.4, 9.9, 9.6, 8.6, 6.9, 6.6, 6.2, 5.9, 5.7, 5.6, 5.5, 5.4, 5.2, 4.95, 4.77, 4.66, 4.62, 4.55, 4.40, 4.29, 4.20, 4.11, 4.02, 3.88, 3.67, 3.61, 3.49, 3.31, 3.18, 3.05, 2.99, 2.85, 2.80, 2.69, 2.62, 2.40 y 2.33Å.

12. Un proceso para la producción de un compuesto según se reivindicó en una de las reivindicaciones 1 a 11, que comprende el melagatran cristalizante.

13. Un proceso según se reivindicó en la reivindicación 12 que comprende melagatran cristalizante a partir de un solvente.

14. Un proceso según se reivindicó en la reivindicación 13, donde el solvente se selecciona del grupo: acetato de alquilo de cadena corta, alcoholes de alquilo de cadena corta, hidrocarburos alifáticos y aromáticos, dialquil éteres, dialquil cetonas, acetonitrilo, soluciones acuosas o mezclas de las anteriores.

15. Un proceso según se reivindicó en la reivindicación 14 donde el solvente se selecciona a partir del grupo: alquil acetatos C₁₋₆, alquil alcoholes C₁₋₆, hidrocarburos alifáticos C₅₋₁₂, hidrocarburos aromáticos C₆₋₁₀, di-alquil éteres C₁₋₆, di-alquil cetonas C₁₋₆, acetonitril, agua o sus mezclas.

16. Un proceso según se reivindicó en la reivindicación 15 donde el solvente se selecciona a partir del grupo: etil acetato, etanol, iso-propanol, iso-octano, n-heptano, tolueno, di-iso-propil eter, metil iso-butil cetona, acetonitrilo, agua o sus mezclas.

17. Un proceso según se reivindicó en una de las reivindicaciones 12 a 16, donde por lo menos un alcohol de alquilo de cadena corta y/o agua se utiliza como solvente y acetonitrilo y/o etil acetato que se utilizan como antisolventes.

18. Un proceso para la producción de un compuesto según se reivindicó en una de las reivindicaciones 7 a 9, que comprende un proceso de acuerdo con una de las reivindicaciones 13 a 17, donde el solvente se encuentra sustancialmente libre de agua.

19. Un proceso para la producción de un compuesto según se reivindicó en una de las reivindicaciones 4 a 6, que comprende un proceso de acuerdo con una de las

reivindicaciones 13 a 17. en la cual el solvente contiene agua.

20. Un proceso para la conversión de una forma cristalina de un compuesto según se reivindicó en una de las reivindicaciones 1 a 3 en otro que comprende la recrystalización de la forma cristalina mencionada inicialmente a partir de un sistema de solventes adecuado.

21. Un proceso para la interconversión de un compuesto anhidrato según se reivindicó en las reivindicaciones 7 o 9, y un compuesto hidrato según se reivindicó en una de las reivindicaciones 4 a 6. que comprende someter el anhidrato cristalino o hidrato (según corresponda) a una atmósfera con un nivel relativo de humedad apropiado.

22. Un compuesto obtenible mediante un proceso de acuerdo con una de las reivindicaciones 12 a 21.

23. Un compuesto según se reivindicó en una de las reivindicaciones 1 a 11 o 22 para utilizarlo como farmacéutico.

24. Una formulación farmacéutica que incluye un compuesto según se reivindicó en una de las reivindicaciones 1 a 11 o 22 en una mezcla con un adyuvante, diluyente o portador farmacéuticamente aceptables.

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25. Una formulación según se reivindicó en la reivindicación 24 que comprende una solución acuosa del compuesto.

26. El uso del compuesto según se reivindicó en una de las reivindicaciones 1 a 11 o 22 en la fabricación de un medicamento para el tratamiento de una condición en la cual se requiere o desea la inhibición de la trombina.

27. Un método de tratamiento de una condición en la cual se requiere o desea la inhibición de la trombina, donde dicho método comprende la administración de una cantidad terapéuticamente eficaz de un compuesto de acuerdo con una de las reivindicaciones 1 a 11 o 22 a un paciente que necesite del mencionado tratamiento.


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia

NOTAS DEL TRADUCTOR OFICIAL:

1. EL CONSULADO DE COLOMBIA (ESTOCOLMO, SUECIA)

Fecha: 2000-06-09

No. 002017

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 PUBLICO, de Estocolmo, Suecia.

MARIA SMITH RUEDA

Encarga de las Funciones Consulares

(Hay firma y sello)

2. MINISTERIO DE RELACIONES EXTERIORES

No. 087641

Fecha: Junio 29 del 2.000.

Cuya firma aparece en el documento desempeña las funciones indicadas.

Jefe de Legalizaciones, Santafé de Bogotá D.C.

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.

Santafé de Bogotá D.C., Junio 30 del 2000.


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia

MINISTERIO DE RELACIONES
EXTERIORES

291438
GABRIEL RUEDA
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS.

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2000 JUL -5 A 8:55

Belgeria
SECRETARÍA DE LEGALIZACIONES
SECRETARÍA DE ROYAL D.C.

PRVPATENT- OCH REGISTRERINGSVERKET
Patentavdelningen**Intyg
Certificate**

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 Astra AB, Södertälje SE
Applicant (s)

(21) Patentansökningsnummer 9902550-4
Patent application number

(86) Ingivningsdatum 1999-07-02
Date of filing

Stockholm, 2000-05-25

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

Emma Högberg
Emma Högberg

Avgift
Fee 170:-



La infrascrita Anno-Maria Bando, Notario Público de Estocolmo, Suecia, certifica que

Emma Högberg,
autorizado para firmar en nombre de la
PRV, Dirección Nacional de Patentes
y Registros,
ha otorgado y firmado el documento que antecede.
Derechos 250.- Estocolmo, 2000-06-07
Coronas De oficio:

[Signature]

REPUBLICA DE COLOMBIA EN

2000-06-09

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apoc

Aune-Marie Soude, Notario Publico.
Estadano, Suecia

M. Smith R.

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO

Impuesto de Timbre

Siete dólares US\$ 7

Derechos Consulares

Quince dólares US\$ 15

NO SE ASUME
RESPONSABILIDAD DEL T. A.

2000 JUN 29 A 14:31

RECEPCIONIZACION
DE DOCUMENTOS

PARA TRAMITACION
EXTERIORES

087641

CUYA FIRMA DEL T. A. EL
DOCUMENTO EN LA
LAS FUNCIONES CONSULARES

NEW CRYSTALLINE FORMS

Field of the Invention

- 5 This invention relates to new solid state forms of a drug, to pharmaceutical compositions containing them, and to processes for obtaining them.

Background of the invention

- 10 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 view of subsequent manufacture of pharmaceutical formulations
- 15 comprising the active compound.

- Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient. This is of particular
- 20 importance in the manufacture of compositions comprising antithrombotic agents.

- Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and
- 25 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, provide for unreliable solubility, and are often found to be unstable and chemically impure.

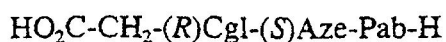
The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved.

Thus, in the manufacture of commercially viable, and pharmaceutically acceptable, drug compositions, it is important, 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.

Prior Art

International patent application WO 94/29336 discloses a number of compounds, which are useful as inhibitors of serine proteases, such as thrombin, including the compound,



wherein Cgl represents cyclohexylglycine, Aze represents azetidine-2-carboxylate and Pab-H represents 4-aminomethylamidinobenzene. The compound is also known as melagatran (glycine, *N*-[(1*R*)-2-[(2*S*)-2-[[[4-

(aminoiminomethyl)phenyl)methyl]amino]carbonyl]-1-azetidiny]-1-cyclohexyl-2-oxoethyl]-).

A process for the synthesis of this compound is described in Example 1 of
5 WO 94/29336, where it is obtained as crude material, by evaporation of reaction solvent following a final deprotection step. The compound is thus isolated in an amorphous form.

Whether it is possible to provide melagatran in a crystalline form is not
10 disclosed in WO 94/29336. Furthermore, no information is provided in relation to how this compound may be obtained in such a form and, more particularly, how it may be obtained in a chemically, and/or solid state, stable form.

15 Disclosure of the Invention

We have found that melagatran may be readily obtained in one or more forms that are both substantially crystalline and stable in nature.

20 Thus, according to a first aspect of the invention there is provided melagatran in a substantially crystalline form (hereinafter referred to as "the compounds of the invention").

Although we have found that it is possible to produce melagatran in forms
25 which are greater than 80% crystalline, by "substantially crystalline" we include greater than 20%, preferably greater than 30%, and more preferably greater than 40% crystalline. The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman

spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

The compounds of the invention may be in the form of a solvate, a hydrate or a mixed solvate/hydrate. Solvates may be of one or more
5 organic solvents, such as lower alkyl (e.g. C₁₋₄ alkyl) alcohols (e.g. methanol, ethanol or *iso*-propanol) or mixtures thereof.

We have found that the compounds of the invention have a surprisingly
10 improved stability when compared with melagatran prepared as described in WO 94/29336.

According to a further aspect of the invention, there is thus provided a stable form of melagatran.

15

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that the compound can be stored in an
20 isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

25 By "solid state stability", we include that the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, solid

state phase transition, hydration, dehydration, solvation or desolvation).

Examples of "normal storage conditions" include temperatures of between
5 minus 80 and plus 50°C (preferably between 0 and 40°C and more
preferably ambient temperature, such as between 15 and 30°C), pressures
of between 0.1 and 2 bars (preferably atmospheric pressure), and exposure
to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or
equal to six months). Under such conditions, compounds of the invention
10 may be found to be less than 15%, more preferably less than 10%, and
especially less than 5%, chemically degraded/decomposed, or solid-state
transformed, as appropriate. The skilled person will appreciate that the
above-mentioned upper and lower limits for temperature and pressure
represent extremes of normal storage conditions, and that certain
15 combinations of these extremes will not be experienced during normal
storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

The term "normal storage conditions" may also include relative humidities
of between 5 and 95% (preferably 10 to 75%). However, in the case of
20 certain crystalline forms according to the invention, changes in
conformation or crystal structure by hydration and/or dehydration may
occur as a result of prolonged exposure to certain extremes of relative
humidities, at normal temperatures/pressures. For example, we have
found that crystalline forms of melagatran that are in the form of a hydrate
25 (e.g. a monohydrate) may be stored at 10% relative humidity or above at
ambient temperature/atmospheric pressure with an insignificant degree of
dehydration. However, we have also found that crystalline forms of
melagatran that are in the form of an anhydrate should be stored at less
than 40% (preferably less than 30%, more preferably less than 20%)

relative humidity at ambient temperature/atmospheric pressure, to maintain an insignificant degree of hydration.

Thus, although compounds of the invention possess a greater solid state stability than forms of melagatran described in the prior art, some compounds of the invention are more solid state stable than others. In this respect, it will be appreciated by the skilled person that storage conditions may be tailored to suit the crystalline form that is being stored.

10 The compounds of the invention may be obtained advantageously by crystallising melagatran.

According to a further aspect of the invention, there is provided a process for the production of a compound of the invention which comprises
15 crystallising melagatran.

Although melagatran may be crystallised with or without the presence of a solvent system (e.g. crystallisation may be from a melt, under supercritical conditions, or achieved by sublimation), we prefer that the
20 crystallisation is from an appropriate solvent system.

We have found that it is possible to obtain crystalline melagatran *via* crystallisation advantageously following dissolution and/or suspension of the compound, or, more advantageously, from reaction solutions within
25 which the compound has been formed.

The solvent system may include one or more organic solvents, such as alkyl acetates (e.g. linear or branched C₁₋₆ alkyl acetates, such as ethyl acetate, *iso*-propyl acetate and butyl acetate), lower (e.g. linear or

- branched C₁₋₆, preferably C₂₋₄) alkyl alcohols (e.g. ethanol, *iso*-propanol), aliphatic and aromatic hydrocarbons (e.g. *iso*-octane, *n*-heptane and toluene), dialkyl ketones (e.g. methyl ethyl ketone and methyl *iso*-butyl ketone), dialkyl ethers (e.g. di-*iso*-propyl ether) and acetonitrile.
- 5 Mixtures of any of the above-mentioned solvents may be used. Organic solvents may also be admixed with water or aqueous solutions.

Different crystalline forms may have different solubilities in different organic solvents at any given temperature. In this respect, above-mentioned solvents may be employed as "antisolvents" (i.e. a solvent in
10 which compounds of the invention are poorly soluble), and may thus aid the crystallisation process. Lower alkyl alcohols are preferred solvents. When lower alkyl alcohols are employed as solvent, other solvents identified above may be employed as antisolvents (especially acetonitrile
15 and ethyl acetate).

When the crystallisation takes place from a reaction solution in which melagatran has been formed, suitable solvents include lower alkyl alcohols (e.g. methanol, ethanol or *iso*-propanol) which may be in admixture with
20 water.

Crystallisation of compounds of the invention from an appropriate solvent system may be achieved by attaining supersaturation in a solvent system which comprises melagatran (e.g. by cooling, by solvent evaporation,
25 and/or *via* the addition of a suitable antisolvent). Crystallisation may also be effected by decreasing the solubility of the substance by the addition of a salt (such as NaCl).

The skilled person will appreciate that the concentration in solution of the compound that is to be crystallised, and the solvent system that is used, may influence crystallisation temperatures and crystallisation times.

- 5 The compounds of the invention may be in the form of a solvate, a hydrate or a mixed solvate/hydrate.

Compounds of the invention may also be in the form of an anhydrate. (The term "anhydrate", when used in this context, also includes
10 compounds that are "ansolvates".) To ensure that anhydrate is produced, the solvent from which the crystallisation occurs should be dried, either before or during the crystallisation process, in order to reduce the water content below a critical level, which should preferably not be exceeded during the crystallisation. Solvent may be dried during the crystallisation
15 process, for example by decreasing the water content of a mixture of the compound to be crystallised and an appropriate organic solvent/aqueous solvent system (e.g. by increasing the amount of organic solvent that is present and/or removal of water by formation of an azeotrope, with successive distillations). The "critical level" of water depends upon
20 factors such as temperature, concentration in solution of the compound to be crystallised, impurity profile, and the solvent system which is employed, but may be determined non-inventively.

Thus, anhydrate may be produced by crystallisation from a solvent
25 system, including one or more organic solvents (such as lower (e.g. C₂₋₆) alkyl alcohols (e.g. ethanol, *iso*-propanol), acetonitrile and/or ethyl acetate) and/or water, which solvent system is, or is rendered during the crystallisation process, substantially free of water. By "substantially free of water", we include that the water content in the solvent system is below

that which will result in the formation of, at most, 20% monohydrate, for any particular solvent system and set of crystallisation conditions.

To ensure that monohydrate is produced, water must be present in the solvent from which the crystallisation occurs. The water content should preferably be above a critical level during the crystallisation (which "critical level" will depend upon the factors mentioned above in respect of production of anhydrate). Thus, crystalline monohydrate may be prepared by crystallising melagatran from a solvent system comprising water, and/or one or more organic solvents, including ethyl acetate, ethanol, *iso*-propanol, methyl *iso*-butyl ketone, methyl ethyl ketone, acetonitrile and mixtures thereof.

To ensure that a solvate is produced, an appropriate organic solvent, capable of forming a solvate, must be present as part of the solvent system from which the crystallisation occurs. Solvates that are in the form of "mixed" solvate/hydrate may also be prepared. For example, we have found that mixed lower alkyl (e.g. C₁₋₄ alkyl) alcohol (e.g. methanol, ethanol and/or *iso*-propanol) solvate/hydrates may be prepared by crystallising a compound of the invention from a mixture of lower alkyl alcohols (e.g. methanol, ethanol and/or *iso*-propanol), water and an antisolvent (e.g. acetonitrile), for example as described hereinafter.

According to a further aspect of the invention, there is provided a compound of the invention that is in the form of a solvate, a compound of the invention that is in the form of a monohydrate, a compound of the invention that is in the form of a mixed lower (e.g. C₁₋₄) alkyl alcoholate/hydrate (e.g. an *iso*-propanol solvate/hydrate), and a compound of the invention that is in the form of an anhydrate. -

As may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallisation process. Under certain thermodynamic conditions (solvent system, temperature and pressure), one crystalline form may be more stable than another. However, other crystalline forms may be kinetically-favoured. Thus, in addition, kinetic factors, such as time, concentration, impurity profile, agitation, the presence of seeds, etc. may also influence which forms appear. Thus, the procedures discussed herein may be adapted by the skilled person as appropriate in order to obtain different crystalline forms of melagatran.

Compounds of the invention that are anhydrides contain no more than 3%, preferably 1% and more preferably 0.5% (w/w) water, whether such water is bound (crystal water or otherwise) or not. Solvates, hydrates and mixed hydrates/solvates contain no less than 0.5 mol of solvent and/or water (as appropriate) per mol of compound of the invention.

Preferred compounds of the invention are those that are in the form of a hydrate, such as a monohydrate. According to a further aspect of the invention, there is provided a compound of the invention that contains at least 0.5, preferably 0.85 and more preferably 0.90 mol water per mol of melagatran, whether such water is bound (crystal water or otherwise) or not.

We have also found that compounds of the invention in one crystalline form can be converted into other crystalline forms. For example, crystalline monohydrate may also be formed by elutriation of other crystalline forms (e.g. anhydrides and/or other solvates) in water or a

mixture of a sufficient amount of water and one or several organic solvents (such as ethanol, *iso*-propanol, ethyl acetate, acetonitrile or methyl *iso*-butyl ketone). The slurry that is formed may preferably be seeded with crystals of the crystalline monohydrate in order to ensure that
5 an appropriate transformation takes place.

Further, drying temperature and drying time may affect the solid state properties and/or the solid state form of compounds of the invention (e.g. solvates, hydrates or mixtures thereof). For example, in the case of
10 hydrates, dehydration may occur at low humidities and/or elevated temperatures and/or reduced pressure. For example, following the formation of crystalline monohydrate, there is a critical humidity level below which drying may be performed, which may result in crystal water being lost, and a solid state transformation to an anhydrate occurring.
15 Conversely, anhydrides may be converted (completely or partially) to monohydrates in cases where they are subjected to an atmosphere with a relative humidity that is sufficiently high.

Thus, according to a further aspect of the invention, there is provided a
20 process for the conversion of one crystalline form of a compound of the invention to another, which comprises recrystallising a compound of the invention from an appropriate solvent system, and/or, in the case of interconversion of anhydrate and monohydrate, subjecting the crystalline anhydrate or monohydrate (as appropriate) to an atmosphere with an
25 appropriate relative humidity level.

The preparation, and characterisation, of *inter alia* anhydrate, monohydrate, and solvate/hydrate forms of compounds of the invention, are described hereinafter. Different crystalline forms of the compounds of

the invention (e.g. the anhydrate and the monohydrate) may be readily characterised using X-ray diffraction methods, for example as described hereinafter.

- 5 Compounds of the invention may be isolated using techniques which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

We have found that, by employing the crystallisation process as described
10 herein, it is possible to produce compounds of the invention with a chemical purity which is above that of the melagatran which is to be isolated in the first instance.

Further purification of compounds of the invention may be effected using
15 techniques which are well known to those skilled in the art. For example impurities may be removed by way of recrystallisation from an appropriate solvent system (e.g. lower alkyl alcohol, such as ethanol or *iso*-propanol), which may include antisolvent (e.g. *iso*-octane, acetonitrile, ethyl acetate, methyl ethyl ketone), water, or a combination of these
20 solvents. Suitable temperatures and times for the recrystallisation depend upon the concentration in solution of the compound to be crystallised, and upon the solvent system which is used.

When compounds of the invention are crystallised, or recrystallised, as
25 described herein, the resultant compound is in a form which has the improved chemical and solid state stability mentioned hereinbefore.

Pharmaceutical Preparations and Medical Use

In accordance with the invention, the compounds of the invention may be administered orally, intravenously, subcutaneously, buccally, rectally, 5 dermally, nasally, tracheally, bronchially, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the compound of the invention in a pharmaceutically acceptable dosage form. However we prefer that the compound of the invention is a form which is suitable for oral or parenteral, such as subcutaneous, 10 administration.

Depending on the disorder, and the patient to be treated, as well as the route of administration, the compounds may be administered at varying doses.

15

According to a further aspect of the invention, there is provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Suitable formulations include those disclosed in international patent 20 applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/39770, WO 97/45138 and WO 98/16252 and unpublished co-pending Swedish patent application No. SE 9802938-2.

The compounds of the invention may be further processed before being 25 admixed with a suitable carrier, diluent or adjuvant. For example, the crystalline form may be milled or ground into smaller particles.

We prefer that formulations comprising compounds of the invention are in a form that is suitable for parenteral (e.g. subcutaneous) delivery. In this

respect, compounds of the invention can be admixed with an aqueous solvent carrier system (see, for example, unpublished co-pending Swedish patent application No. SE 9802938-2) in order to provide a pharmaceutical formulation that is in the form of a liquid and/or a solution.

5

The amount of compound of the invention which is employed in such a formulation will depend on the condition, and patient, to be treated, as well as the compound(s) which is/are employed, but can be determined non-inventively.

10

The compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

- 15 In particular, the compounds of the invention are potent inhibitors of thrombin, for example as demonstrated in the tests described in WO 94/29336. The compounds of the invention are expected to be useful in the treatment of conditions where inhibition of thrombin is required or desirable, including those described in, for example WO 94/29336 and
- 20 WO 97/23499, the disclosures in which documents are hereby incorporated by reference.

- Suitable doses of the compound of the invention in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients are in
- 25 the range 0.4 to 40 mg per day, and/or 0.0002 to 4 mg/kg (preferably 0.002 to 1 mg/kg) body weight, at parenteral administration, and 2 to 1000 mg per day, and/or 0.001 to 100 mg/kg (preferably 0.01 to 25 mg/kg) body weight, at oral administration.

15

According to a further aspect of the invention there is provided a method of treatment of a condition where inhibition of thrombin is required or desired, which method includes administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment, as well as the prophylaxis, of a condition.

Compounds of the invention have the advantage that they are in a form which provides for improved ease of handling. Further, compounds of the invention have the advantage that they may be produced in forms which have improved chemical and solid state stability. Thus, compounds may be stable when stored over prolonged periods.

15

Compounds of the invention may also have the advantage that they may be prepared in good yields, in a higher purity, in less time, more conveniently, and at a lower cost, than forms of melagatran prepared previously.

20

The invention is illustrated, but in no way limited, by the following examples, with reference to the enclosed figures in which:

Figure 1 shows an X-ray powder diffractogram for the crystalline form of melagatran anhydrate obtained by way of Example 2.

Figure 2 shows an X-ray powder diffractogram for the crystalline form of melagatran monohydrate obtained by way of Example 4.

Figure 3 shows an X-ray powder diffractogram for the crystalline form of melagatran anhydrate obtained by way of Example 6.

Figure 4 shows an X-ray powder diffractogram for the crystalline form of melagatran *iso*-propanolate/hydrate obtained by way of Example 10.

General Procedures

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in Giacobazzo, 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 & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & 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.

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

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850 instrument.

Forms prepared in accordance with the Examples below showed "essentially" the same XRPD diffraction patterns and/or DSC thermograms as other Examples disclosed below, when it was clear from

the relevant patterns/thermograms (allowing for experimental error) that the same crystalline form had been formed. Thus, limits of experimental error for DSC onset temperatures may be in the range $\pm 5^{\circ}\text{C}$ (e.g. $\pm 2^{\circ}\text{C}$), and for XRPD distance values may be in the range ± 2 on the last decimal place.

Synthesis of Melagatran Monohydrate

Example 1

10

(a) Boc-(R)Cgl-(S)Aze-Pab-Z

DMAP (3.0 eq.) and Boc-(R)Cgl-(S)Aze-OH (1.0 eq.) were dissolved in ethyl acetate:acetonitrile (80:20 v/v) at a volume of 18 L/kg of Boc-(R)Cgl-(S)Aze-OH at 20°C . Pab-Z x HCl (1.15 eq.) was charged into the resultant solution. EDAC x HCl (1.4 eq.) was added, and the slurry was stirred at 25°C for about 3 hours. A sample was removed for in-process control. The reaction solution was worked up when at least 95% conversion was determined to have taken place. The slurry was then filtered, and the filter cake was washed with ethyl acetate:acetonitrile (80:20 v/v). Aqueous sodium chloride solution (10% w/w) was added and the pH was adjusted to 4.0 with hydrochloric acid solution (4 M). The solution was thoroughly stirred for at least 15 minutes. The water phase was separated off and the organic phase was extracted with aqueous sodium chloride solution (20% w/w). The solution was thoroughly stirred for at least 15 minutes. The water phase was separated off and the organic phase extracted with aqueous sodium chloride solution (10% w/w). The pH was adjusted to 8.0 with aqueous potassium carbonate solution (25% w/w). The solution was thoroughly stirred for at least 15 minutes. The water phase was separated off. Ethyl acetate and

acetonitrile were evaporated under vacuum (ca. 15 kPa) at temperature of ca. 40°C, until the volume in the reactor was approximately 8 L/kg of starting material. More ethyl acetate (13 L/kg of starting material) was added during the evaporation process. A sample was removed for water content analysis. Ethyl alcohol (10% v/v of the total volume) was then added. The solution was used directly in the next step.

(b) H-(R)Cgl-(S)Aze-Pab-Z

The solution from step (a) was cooled to 10°C. Methane sulphonic acid (7 eq. per eq. of Boc-(R)Cgl-(S)Aze-Z) was charged, maintaining the temperature below 20°C. The temperature was adjusted to 22°C and the reaction solution stirred (4 hours) until at least 95% conversion had occurred (as determined by HPLC). The reaction solution was cooled to 10°C and extracted with a cooled (10°C) 25% (w/w) aqueous potassium carbonate solution (8 eq. K₂CO₃) for at least 15 minutes. The temperature was adjusted to 20°C and the water phase was separated off. The organic phase was washed with a mixture of aqueous sodium chloride solution (10% w/w) and potassium carbonate (1 eq. K₂CO₃) for at least 15 minutes. The water phase was separated off. The solution of the subtitle compound was used directly in the next step.

(c) Bzl-OC(O)-CH₂-(R)Cgl-(S)Aze-Pab-Z

To the reaction solution from step (b) above, further ethyl acetate, water and potassium carbonate (3.0 eq. per eq. of H-(R)Cgl-(S)Aze-Pab-Z) were charged, and the reaction mixture was stirred until the potassium carbonate dissolved. Benzyl bromoacetate (1.2 eq. per eq. of H-(R)Cgl-(S)Aze-Pab-Z) was added and the reactor temperature was increased to 40°C. The temperature was maintained for about 20 hours. A sample was removed for analysis by HPLC. When 95% conversion had

occurred, the temperature was decreased to 20°C and the reaction mixture was allowed to settle for at least 20 minutes. The water phase was separated off and the solution cooled to 10°C. Aqueous sodium chloride solution (4% w/w) was added and the pH adjusted to 4.0 with 4 M hydrochloric acid solution. The two-phase system was thoroughly mixed for at least 15 minutes and allowed to separate for at least 20 minutes. The water phase was separated off. Sodium chloride solution (4% w/w) was added and the pH adjusted to 4.0 with 4 M hydrochloric acid solution. The solution was thoroughly mixed for at least 15 minutes and allowed to separate for at least 20 minutes. The water phase was separated off. Water was added to the resultant solution, which was cooled to 10°C. The pH was adjusted to 2.5 with 4 M hydrochloric acid solution. The two-phase system was thoroughly stirred for at least 15 minutes and allowed to separate for at least 20 minutes. The water phase was separated and charged slowly into a mixture of potassium carbonate in ethyl acetate. The pH was adjusted to 7.0 with 25% (w/w) aqueous potassium carbonate solution and the reaction mixture was thoroughly mixed for at least 15 minutes at 20°C and allowed to separate for at least 20 minutes. The water phase was separated off. Ethyl acetate was evaporated under vacuum (*ca.* 10 kPa) at a maximum temperature of 40°C until the volume in the reaction vessel was about 8.5 L/kg of Boc-(*R*)Cgl-(*S*)Aze-OH). More ethyl acetate was added (5 L/kg of Boc-(*R*)Cgl-(*S*)Aze-OH) and evaporated again under reduced pressure until the volume in the reaction vessel was about 8.5 L/kg. A sample was taken for water content analysis. If the water content was less than 0.5% (w/v), water was added to give a total water content of 0.5-2.0% (w/v). The temperature was adjusted to 45°C, the reaction solution was seeded with 2% (w/w) of the sub-title compound and the slurry was thoroughly stirred for 10 hours, then cooled to 30°C over 3 hours and subsequently stirred



20

for at least 3 hours. Toluene (5 L/kg of the sub-title compound) was charged and the slurry was stirred for at least 15 minutes. Ethyl acetate and toluene were evaporated under reduced pressure (*ca.* 10 kPa) until the volume was the same as before the toluene addition. Toluene (5 L/kg of the sub-title compound) was added and the slurry was stirred for at least 30 minutes. The ethyl acetate and toluene were evaporated again under reduced pressure until the volume was the same as before the toluene addition. Toluene was then added to a total volume of about 11 L/kg of sub-title compound. The slurry was carefully stirred for at least 3 hours at 20°C. The crystals were filtered off and washed with toluene and dried in vacuum (<150 mbar) at approximately 40°C.

(d) Melagatran Monohydrate

Ethanol was charged into a reactor at 20°C. Pd/C (10% w/w of Bzl-OC(O)-CH₂-(R)Cgl-(S)Aze-Pab-Z), elutriated in water, was added. (The total amount of water was 6% v/v of total solvent.) Bzl-OC(O)-CH₂-(R)Cgl-(S)Aze-Pab-Z (from step (c) above; 8% w/v of total solvent) was charged, and the temperature was raised to 25°C. 3.5 bar pressure of H₂ was applied to the reaction mixture, which was stirred vigorously for 5 h. When the reaction was finished (as determined by HPLC), the temperature was set to 20°C, and the reaction slurry was treated with activated carbon (10% w/w of starting material) elutriated in water (0.5 L/kg of starting material) over 0.5 h. The catalyst and carbon were filtered off and the filter cake was washed with ethanol (5 L/kg of melagatran anhydrate). Ethanol was then evaporated at reduced pressure until the volume was 4 L/kg of melagatran anhydrate. *iso*-Propanol (14 L/kg of melagatran anhydrate) was charged and the solution was again evaporated at reduced pressure (at a temperature between 20 and 30°C) to a volume of about 7 L/kg of melagatran anhydrate. The solution was filtered and washed with

iso-propanol (7 L/kg of melagatran anhydrate). Ethanol/*iso*-propanol were evaporated at reduced pressure (at a temperature between 20 and 30°C) to a volume of about 4.4 L/kg of melagatran anhydrate. The water content was analyzed and adjusted to 0.6 - 0.7 L/kg of melagatran anhydrate. The solution was warmed to 45°C and acetonitrile (6.0 L/kg of melagatran anhydrate) was added over 20 minutes, whereupon crystallization was started by seeding with the title compound (obtained analogously to the method described in Example 4 below; 2% w/w product). The mixture was stirred for about 15 h. Acetonitrile (6.5 L/kg of melagatran anhydrate) was charged into the vessel. The slurry was stirred at 40°C for 3 h, then cooled to 20°C over 1 h and finally stirred at 20°C for at least 1 h. The crystals were isolated by filtration and washed with acetonitrile:*iso*-propanol (9:1 (v/v), 3.5 L/kg of the title compound), acetonitrile (2 L/kg of the title compound) and finally ethyl acetate (3 L/kg of the title compound). The crystals were dried at 40°C and 150-200 mbar.

The crystals were analyzed by XRPD, TGA, GC, DSC and Karl-Fischer titration. They showed essentially the same XRPD pattern, and DSC thermogram, as those exhibited by the form obtained according to Example 4 below.

Crystallisation of Melagatran Anhydrate

25 Example 2

A reaction solution (ethanol:water) containing approximately 64.8 g of melagatran, prepared analogously to the method described in Example 1 above (excluding the last crystallisation step), in a round-bottomed flask, was concentrated by evaporation at reduced pressure until 149 g of

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solution remained. 200 mL of absolute ethanol was then charged into the vessel, and the solution was concentrated again until 89.5 g remained. A white precipitate was formed. A further 250 mL of absolute ethanol was then charged into the vessel, and the slurry was agitated at 30 to 35°C until all of the solute was dissolved. The solution was concentrated again until 78.9 g of solution remained. A further 550 mL of absolute ethanol was added, and the suspension was agitated at 38°C until everything dissolved. The water content was 0.5% (w/w) as determined by Karl-Fischer titration. The solution was filtered, and the filter was washed with 200 mL of absolute ethanol. The solution was heated to 30°C under a N₂-atmosphere, and acetonitrile was charged into the vessel in portions until the solution became opaque (a total of 1380 mL of acetonitrile was charged). The solution was seeded using seed crystals of the title product. The suspension was agitated overnight, and cooled to ambient temperature. The crystals were washed under reduced pressure with 350 mL of a mixture of ethanol and acetonitrile (1:5 (v/v)), and then with acetonitrile (300 mL). The crystals were then dried at 40°C (0.1 mbar). After 4 hours drying, the particles were milled. The drying was then continued under the same conditions as above for an additional 20 hours.

20

The crystals were analyzed by XRPD, GC and Karl-Fischer titration. The XRPD result is tabulated below (Table 1) and is shown in Figure 1.

Karl-Fischer titration showed 1.1% (w/w) water.

25

Table 1

d value (Å)	intensity (%)	d value (Å)	intensity (%)	d value (Å)	intensity (%)
15.9	100	6.0	5	4.08	10
15.1	30	5.8	5	3.97	10
10.9	55	5.5	5	3.82	5
8.9	5	5.3	20	3.76	5
8.4	5	5.0	15	3.66	5
8.0	20	4.87	30	3.44	5
7.0	10	4.81	25	3.32	5
6.8	10	4.71	10	3.20	5
6.4	10	4.61	15		
6.2	5	4.45	5		

Example 3

- 5 85 mL of a reaction solution (ethanol) containing melagatran, prepared analogously to the process described in Example 1 above (excluding the last crystallisation step) was charged into a 500 mL round-bottomed flask. The solution was concentrated by distillation (pressure: 50 mbar; bath temperature: 70°C) until 15.3 g of solution remained. 63 mL of *iso*-
- 10 propanol was added and the solution was concentrated again as above until 14.8 g remained. A sample was withdrawn, and the water content was 0.93% (v/v) as determined by Karl-Fischer titration. An additional 1.16 mL of purified water was added to the solution in order to improve the filtration. The round-bottomed flask was placed in an oil bath, kept at
- 15 40°C and the solution was agitated using an impeller. 30 mL of acetonitrile was charged slowly into the agitated solution. 80 mg of seed crystals of the title compound were added to the solution, which started to

24

crystallize. The suspension was agitated for an additional 14 hours at 40°C and then 23 mL of acetonitrile was added. The agitation was continued at 40°C for 3 hours, the oil bath was then removed, and the suspension was agitated at ambient temperature for 2 hours. The crystals
5 were filtered off under vacuum, washed with a mixture of *iso*-propanol and acetonitrile, then with pure acetonitrile, and then dried at 40°C under reduced pressure. The yield (based on the amount left in the mother liquor) was 84%.

10 The crystals were analyzed by XRPD, GC and Karl-Fischer titration. They showed essentially the same XRPD pattern as that exhibited by the form obtained according to Example 2 above.

Conversion of Crystalline Melagatran Anhydrate to Crystalline Melagatran

15 Monohydrate

Example 4

2 g of melagatran anhydrate (obtained according to the method described in Example 3 above) was charged, together with 1 mL of tap water, 6 mL
20 of *iso*-propanol and 13.2 mL of acetonitrile, into a 50 mL Erlenmeyer flask. The flask was placed on a shaking table and kept at ambient temperature. The crystals were filtered off after 9 days of agitation/shaking using vacuum and thereafter dried at ambient temperature in a fume hood.

25

The crystals were analyzed by XRPD, DSC, TGA, GC and Karl-Fischer titration.

The XRPD result is tabulated below (Table 2) and is shown in Figure 2.

Table 2

d value (Å)	intensity (%)	d value (Å)	intensity (%)	d value (Å)	intensity (%)
21.1	65	5.07	55	3.63	15
10.5	75	4.90	25	3.52	20
7.6	90	4.75	60	3.39	5
7.0	100	4.68	50	3.27	10
6.7	10	4.35	15	3.23	5
6.4	5	4.19	20	3.12	20
6.2	25	4.00	10	3.09	10
5.7	5	3.94	5	3.06	5
5.4	10	3.85	20	2.75	5
5.3	30	3.81	15	2.38	10
5.22	45	3.73	10	2.35	10
5.19	25	3.70	10		

- 5 DSC showed one endotherm with an onset temperature of *ca.* 83°C with an associated heat of -125 J/g (due to dehydration) and one at *ca.* 210°C (due to melting).

- TGA showed a decrease in mass of *ca.* 4.3% around 95°C corresponding
10 to a monohydrate and a decomposition starting around 220°C.

Karl-Fisher titration showed 4.3% (w/w) water.

Example 5

139 kg of ethyl acetate was charged into a reactor together with 10.3 kg of melagatran anhydrate (from Example 9 below), followed by 1.9 kg of purified water (4.5 equivalents). The suspension was agitated for 16-20
5 hours at 40°C. Following cooling to 25°C, the suspension was agitated for an additional 2 days. The slurry was then filtered using pressure filtration, and the reactor and filter cake were washed with 46 kg of ethyl acetate. The crystals were dried at reduced pressure (150 ± 50 mbar) and 40°C for several days.

10

The crystals were analyzed by XRPD, DSC, TGA, GC and Karl-Fischer titration. They showed essentially the same XRPD pattern, and DSC thermogram, as those exhibited by the form obtained according to Example 4 above. Karl-Fischer titration showed a water content of 4.0%
15 (w/w).

Conversion of one Crystalline Form of Melagatran Anhydrate to another Crystalline Form of Melagatran Anhydrate

20 Example 6

2.5 g of melagatran anhydrate (from Example 2 above) was charged, together with 6 mL of *iso*-propanol, 1.0 mL of tap water and 13.2 mL of acetonitrile, into a 50 mL Erlenmeyer flask. The flask was placed on a shaking table, where it was left for 9 days. The crystals were filtered
25 under vacuum and then dried at 40°C and at a pressure of less than 20 mbar overnight.

The crystals were analyzed by XRPD, DSC, GC and Karl-Fischer titration.

The XRPD result is tabulated below (Table 3) and is shown in Figure 3.

DSC showed an endotherm with an extrapolated onset temperature of
5 210°C associated with a heat of -120 J/g.

Table 3

d value (Å)	intensity (%)	d value (Å)	intensity (%)	d value (Å)	intensity (%)
17.8	100	4.43	5	3.28	1
8.9	45	4.38	15	3.24	1
8.1	20	4.33	10	3.17	1
7.5	10	4.14	5	3.09	1
6.9	5	4.12	10	3.01	1
6.3	5	4.05	10	2.96	5
5.9	25	3.91	10	2.83	1
5.6	10	3.73	10	2.54	1
5.5	10	3.61	5	2.49	1
5.4	10	3.58	5	2.41	1
5.3	5	3.56	5	2.38	5
5.2	5	3.47	5	2.35	1
5.0	10	3.40	5		
4.71	10	3.36	5		

Conversion of Crystalline Melagatran Monohydrate to Crystalline
Melagatran Anhydrate

Example 9

- 5 Crystals of monohydrate (from Example 1 above) were dried at reduced pressure (< 15 -20 mbar) and 40°C until the water content was less than 1.0% (w/w).

The crystals were analyzed by XRPD, DSC, GC and Karl-Fischer
10 titration. They showed essentially the same XRPD pattern, and DSC thermogram, as those exhibited by the form obtained according to Example 6 above.

Crystallisation of Melagatran *iso*-Propanolate/Hydrate

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Example 10

- 2.0 g of melagatran anhydrate (from Example 3 above) was added to an Erlenmeyer flask. 5.5 mL of *iso*-propanol, 2.5 mL of ethanol, 1.4 mL of purified water and 24 mL of acetonitrile were then charged into the flask.
20 A magnetic bar was placed in the flask, which was placed on a shaking table, kept at ambient temperature. The suspension was agitated for 7 days. The crystals were filtered under vacuum and then dried at 40°C , at a pressure of less than 20 mbar overnight.
- 25 The crystals were analyzed by XRPD, DSC, TGA, GC and Karl-Fischer titration. The XRPD result is tabulated below (Table 4) and is shown in Figure 4.

Table 4

d value (Å)	intensity (%)	d value (Å)	intensity (%)	d value (Å)	intensity (%)
19.7	25	5.4	15	3.67	10
13.1	100	5.2	25	3.61	5
11.4	95	4.95	5	3.49	15
9.9	35	4.77	5	3.31	5
9.6	10	4.66	45	3.18	5
8.6	40	4.62	25	3.05	5
6.9	60	4.55	10	2.99	5
6.6	10	4.40	25	2.85	5
6.2	15	4.29	35	2.80	5
5.9	15	4.20	15	2.69	5
5.7	20	4.11	25	2.62	1
5.6	15	4.02	20	2.40	5
5.5	15	3.88	15	2.33	5

GC showed 4.0% (w/w) *iso*-propanol and Karl-Fischer titration showed
5 6.5% (w/w) water. The results indicated that a mixed *iso*-
propanolate/hydrate had been formed.

TGA showed a decrease in mass of *ca.* 4.6% around 55°C, and a decrease
in mass of *ca.* 5.6% around 140°C.

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Abbreviations

(S)Aze = (S)-azetidine-2-carboxylate

Boc = *tert*-butyloxycarbonyl

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- Bzl = benzyl
(*R*)Cgl = (*R*)-cyclohexylglycine
DMAP = 4-dimethylaminopyridine
EDAC = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
5 Pab-H = 4-aminomethylamidinobenzene
Z = benzyloxycarbonyl

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Claims

1. A substantially crystalline form of melagatran.
- 5 2. A stable form of melagatran.
3. Melagatran in a form which has a high stability.
4. A compound as claimed in any one of Claims 1 to 3, which is in
10 the form of a hydrate.
5. A compound as claimed in any one of Claims 1 to 3, which
contains at least 0.5 mol of water per mol of melagatran.
- 15 6. A compound as claimed in Claim 4 or Claim 5, characterised by a
differential scanning calorimetry curve, at a heating rate of 10°C/min in a
closed cup with a pinhole under flowing nitrogen, exhibiting an endotherm
with an extrapolated onset temperature of about 83°C and an associated
heat of about -125 J/gram; an X-ray powder diffraction pattern
20 characterised by crystalline peaks with d-values at 21.1, 10.5, 7.6, 7.0,
6.7, 6.4, 6.2, 5.7, 5.4, 5.3, 5.22, 5.19, 5.07, 4.90, 4.75, 4.68, 4.35,
4.19, 4.00, 3.94, 3.85, 3.81, 3.73, 3.70, 3.63, 3.52, 3.39, 3.27, 3.23,
3.12, 3.09, 3.06, 2.75, 2.38 and 2.35 Å; and/or a water content of 4.3%
(w/w).
- 25 7. A compound as claimed in any one of Claims 1 to 3, which is in
the form of an anhydrate.
8. A compound as claimed in Claim 7 characterised by an X-ray

powder diffraction pattern characterised by crystalline peaks with d-values at 15.9, 15.1, 10.9, 8.9, 8.4, 8.0, 7.0, 6.8, 6.4, 6.2, 6.0, 5.8, 5.5, 5.3, 5.0, 4.87, 4.81, 4.71, 4.61, 4.45, 4.08, 3.97, 3.82, 3.76, 3.66, 3.44, 3.32 and 3.20 Å.

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9. A compound as claimed in Claim 7 characterised by a differential scanning calorimetry curve, at a heating rate of 10°C/min in a closed cup with a pinhole under flowing nitrogen, exhibiting an endotherm with an extrapolated onset temperature of about 210°C and an associated heat of about -120 J/g; and/or an X-ray powder diffraction pattern characterised by crystalline peaks with d-values at 17.8, 8.9, 8.1, 7.5, 6.9, 6.3, 5.9, 5.6, 5.5, 5.4, 5.3, 5.2, 5.0, 4.71, 4.43, 4.38, 4.33, 4.14, 4.12, 4.05, 3.91, 3.73, 3.61, 3.58, 3.56, 3.47, 3.40, 3.36, 3.28, 3.24, 3.17, 3.09, 3.01, 2.96, 2.83, 2.54, 2.49, 2.41, 2.38 and 2.35 Å.

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10. A compound as claimed in any one of Claims 1 to 3, which is in the form of a mixed *iso*-propanolate/hydrate.

11. A compound as claimed in Claim 10, characterised by an X-ray powder diffraction pattern characterised by crystalline peaks with d-values at 19.7, 13.1, 11.4, 9.9, 9.6, 8.6, 6.9, 6.6, 6.2, 5.9, 5.7, 5.6, 5.5, 5.4, 5.2, 4.95, 4.77, 4.66, 4.62, 4.55, 4.40, 4.29, 4.20, 4.11, 4.02, 3.88, 3.67, 3.61, 3.49, 3.31, 3.18, 3.05, 2.99, 2.85, 2.80, 2.69, 2.62, 2.40 and 2.33 Å.

25

12. A process for the production of a compound as claimed in any one of Claims 1 to 11, which comprises crystallising melagatran.

13. A process as claimed in Claim 12, which comprises crystallising melagatran from a solvent.

14. A process as claimed in Claim 13, wherein the solvent is selected
5 from the group: lower alkyl acetates, lower alkyl alcohols, aliphatic and aromatic hydrocarbons, dialkyl ethers, dialkyl ketones, acetonitrile, aqueous solutions, or mixtures thereof.

15. A process as claimed in Claim 14 wherein the solvent is selected
10 from the group: C₁₋₆ alkyl acetates, C₁₋₆ alkyl alcohols, C₅₋₁₂ aliphatic hydrocarbons, C₆₋₁₀ aromatic hydrocarbons, di-C₁₋₆ alkyl ethers, di-C₁₋₆ alkyl ketones, acetonitrile, water, or mixtures thereof.

16. A process as claimed in Claim 15 wherein the solvent is selected
15 from the group: ethyl acetate, ethanol, *iso*-propanol, *iso*-octane, *n*-heptane, toluene, di-*iso*-propyl ether, methyl *iso*-butyl ketone, acetonitrile, water, or mixtures thereof.

17. A process as claimed in any one of Claims 12 to 16, in which at
20 least one lower alkyl alcohol and/or water is used as solvent and acetonitrile and/or ethyl acetate is/are used as antisolvent.

18. A process for the production of a compound as claimed in any one
of Claims 7 to 9, which comprises a process according to any one Claims
25 13 to 17, in which the solvent is substantially free of water.

19. A process for the production of a compound as claimed in any one
of Claims 4 to 6, which comprises a process according to any one Claims
13 to 17, in which the solvent contains water.

20. A process for the conversion of one crystalline form of a compound as claimed in any one of Claims 1 to 3 to another which comprises recrystallising that first-mentioned crystalline form from an appropriate solvent system.

21. A process for the interconversion of an anhydrate compound as claimed in Claim 7 or Claim 9, and a hydrate compound as claimed in any one of Claims 4 to 6, which comprises subjecting the crystalline anhydrate or hydrate (as appropriate) to an atmosphere with an appropriate relative humidity level.

22. A compound obtainable by a process according to any one of Claims 12 to 21.

23. A compound as claimed in any one of Claims 1 to 11 or 22 for use as a pharmaceutical.

24. A pharmaceutical formulation including a compound as claimed in any one of Claims 1 to 11 or 22 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

25. A formulation as claimed in Claim 24, which comprises an aqueous solution of the compound.

26. The use of compound as claimed in any one of Claims 1 to 11 or 22 in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required or desired.

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27. A method of treatment of a condition where inhibition of thrombin is required or desired which method comprises administering a therapeutically effective amount of a compound according to any one of Claims 1 to 11 or 22 to a patient in need of such treatment.

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ABSTRACT

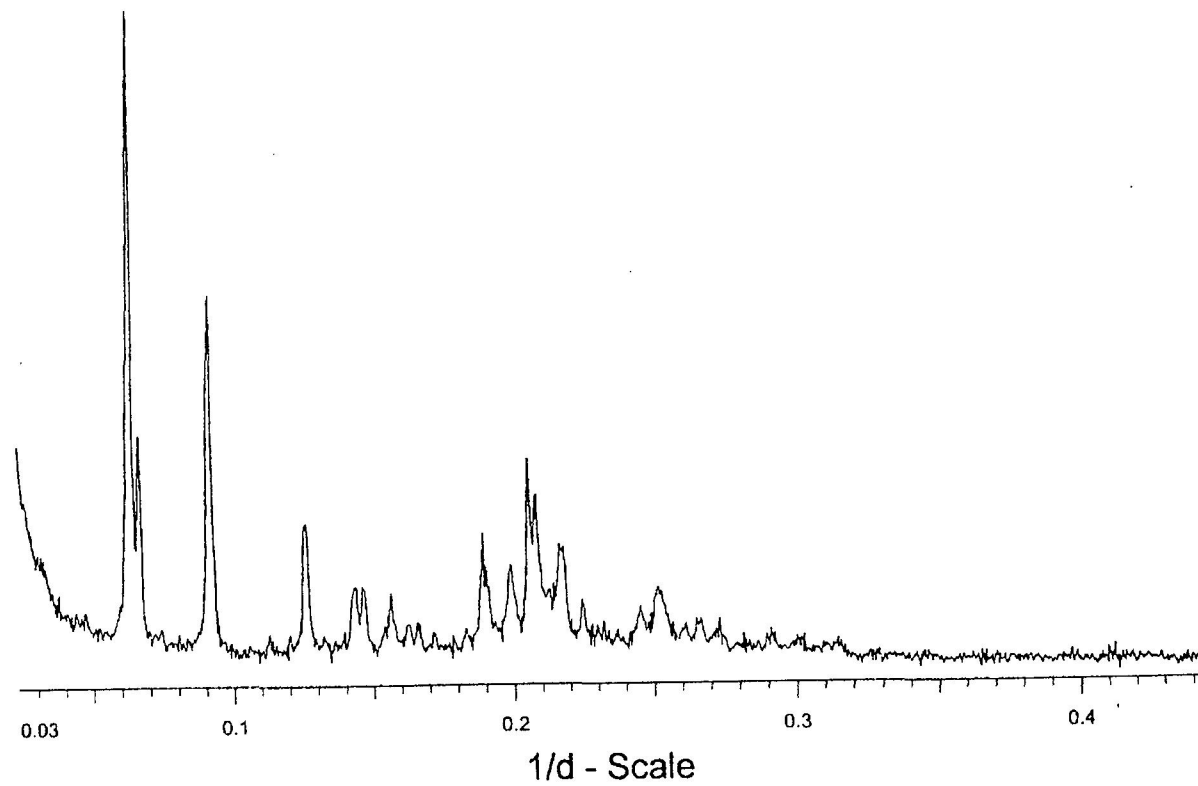
There is provided melagatran in a form which is substantially crystalline.
It has been found that crystalline forms of melagatran have a high
5 chemical and solid state stability when compared to amorphous forms of
the compound.

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Figure 1



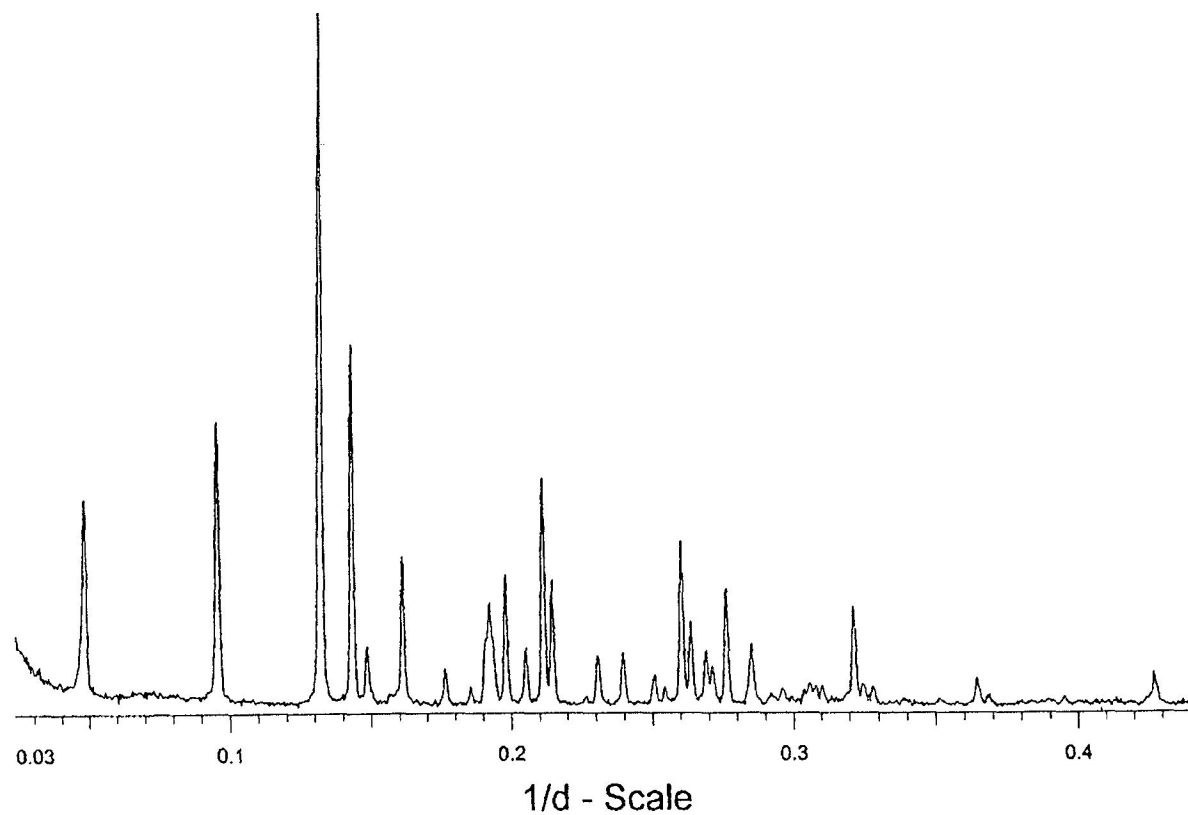
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Figure 2



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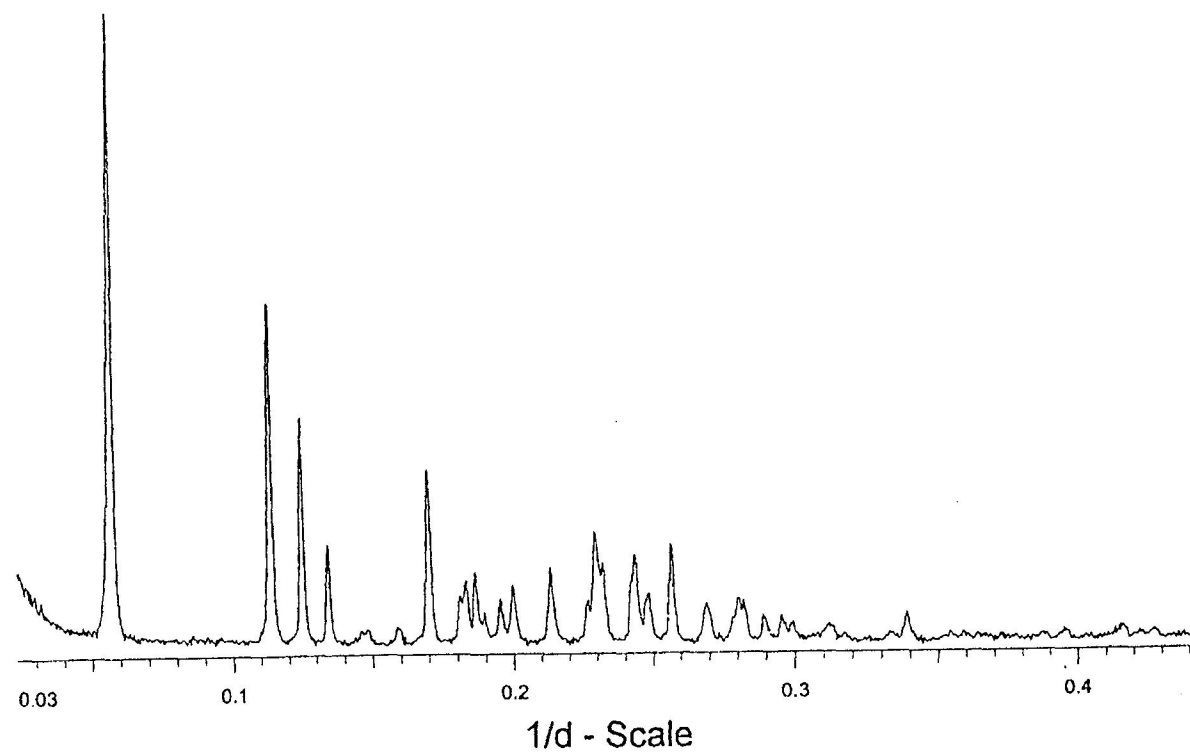
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Figure 3



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NO SE ASISTE
A LA REUNION
DEL 11 DE JULIO
DE 1964
POR
FALTA DE
ASISTENCIA
DE LA LEGALIZACION
DE LA LEGALIZACION
DE LA LEGALIZACION

INFORME
DE LA
REUNION
DEL 11 DE JULIO
DE 1964
POR
FALTA DE
ASISTENCIA
DE LA LEGALIZACION
DE LA LEGALIZACION
DE LA LEGALIZACION

CERTIFICADO NOTARIAL (INDIVIDUO)

NOTARIAL CERTIFICATE (INDIVIDUAL)

A los 21 días del mes de Junio
2000, comparecí personalmente ante mi,
Notario Publico,

On this 21 day of Junio 2000
19 personally appeared before me, a Notary Public,

LENA HEDSTRÖM,
ANITA LUNDBLAD y
SOFIA NAGARD

Lena Hedstrom,
Anita Lundblad y
Sofia Nagard

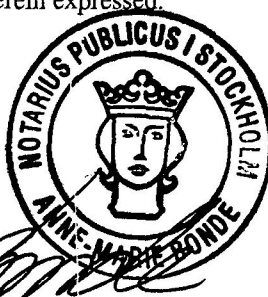
a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarado ante mí que
otorga el mismo para los fines y propósitos que
en él se expresan.

to me known and known to me to be the person
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Anne-Marie Bonde

Anne-Marie Bonde



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ESTOCOLMO, SUECIA

2000 -06- 27

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Previa la confrontación correspondiente D.
FE de que la firma que aparece en este docu-
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Estocolmo, Suecia

M. Smith
MARIA SMITH RUEDA
Encargada de las Funciones Consulares

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ASSIGNMENT

The undersigned,

Lena Hedström

domiciled in

AstraZeneca R&D Södertälje, S-151 85 Södertälje,
Sweden and

Anita Lundblad and Sofia Nägård both
Domiciled in

AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden

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

NEW CRYSTALLINE FORMS

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

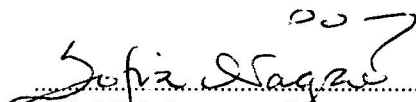
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S-151 85 Södertälje, Sweden

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.


Lena Hedström


Anita Lundblad


Sofia Nägård

TRASPASO

abajo firmado

Lena Hedstrom

domiciliado en

AstraZeneca R&D Söldertälje, S151 85
Söldertälje, Suecia y

Anita Lundblad y Sofia Nagard
domiciliadas en

AstraZeneca R&D Mölndal, S-143, Suecia

declamos bajo juramento ser único y verda-
deros inventores de.

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