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(54) **Novel crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido)-3-vinyl-3-cephem-4-carboxylic acid (syn isomer).**

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(73) Proprietor: **FUJISAWA PHARMACEUTICAL CO., LTD.**
3, Doshomachi 4-chome
Higashi-ku
Osaka-shi
Osaka 541 (JP)

(72) Inventor: **Takaya, Takao**
5-87, Suimeidai 1-chome
Kawanishi-shi
Hyogo 666-01 (JP)
Inventor: **Shirai, Fumiyuki**
2-10, Midorigaoka 2-chome
Ikeda-shi
Osaka 563 (JP)
Inventor: **Nakamura, Hitoshi**
244-1, Aogein
Mino-shi
Osaka 562 (JP)
Inventor: **Inaba, Yasunobu**
2-6-504, Kitamidorigaoka 1-chome
Toyonaka-shi
Osaka 560 (JP)

(74) Representative: **Türk, Dietmar, Dr. rer. nat.**
Türk, Gille, Hrabal, Leifert
Patentanwälte
Brucknerstrasse 20
D-40593 Düsseldorf (DE)

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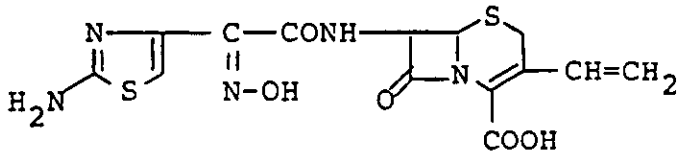
Description

The present invention relates to novel crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) [hereinafter referred to as "the compound (I)" in the present specification] as shown by the following formula (I):



(I)

processes for its preparation and pharmaceutical compositions containing it.

The compound (I), which is a very useful antimicrobial agent, is a known compound and was described, for example, in U.S. Patent 4,559,334 as the object compounds of Examples 14 and 16.

Our further experimental investigation revealed that the compound (I) each prepared according to the procedure of said Examples 14 and 16 in said U.S. Patent 4,559,334 was a crystalline-like amorphous product, not a crystalline product. However, the amorphous product has the disadvantages that it is bulky, not so pure, unstable and insufficient in filtration rate. Therefore, it is not suitable for a pharmaceutical product or is not easy to handle in pharmaceutical preparations, in producing it in a large scale or in storage.

After an intensive study, the inventors of the present invention succeeded in obtaining the compound (I) as a special crystalline form, i.e. Crystal A, and completed the present invention, which is explained in detail as follows.

According to a first aspect the present invention relates to the compound (I) per se having the above formula.

Physicochemical Properties of Crystal A of The Compound (I)

The physico-chemical properties of Crystal A of the compound (I) provided by the present invention are explained in the following.

1) Crystal Form

prisms

2) Powder X-Ray Diffraction Pattern

Crystal A of the compound (I) shows its distinguishing peaks at the diffraction angles [2θ (°)] as shown in the following table, the measurement condition being as follows:
Target: Cu Filter: Ni
Voltage: 30 kV Current: 10 mA
Detector: Scintillation Counter

2 θ (°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.4
about 28.0

According to a second aspect the present invention relates to processes for preparing the compound (I) as defined below.

The Process For Preparing Crystal A of The compound (I)

In the following, the process for the preparation of Crystal A of the compound (I) of the present invention is explained in detail.

Crystal A of the compound (I) can be obtained by dissolving the compound (I) in an alcohol (preferably methanol), continuing to stir this solution slowly under warming (preferably below 40 • C), preferably after the addition of water warmed at almost the same temperature as that of said solution, then cooling this solution to room temperature and allowing it to stand.

During the crystallization of Crystal A, it is preferable to keep the condition of slightly beyond the saturation.

Crystal A of the compound (I) obtained according to aforesaid process can be collected by filtration and dried by means of the conventional methods.

The water content of Crystal A of the compound (I) obtained above is about 0.8% (measured by Karl Fisher method).

According to a third aspect the present invention relates to a pharmaceutical composition containing the crystalline compound (I) as defined above as active ingredient in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

According to further aspects the present invention relates to the use of the crystalline compound (I) as defined above for manufacture of a medicament for treating or preventing infectious diseases; to the crystalline compound (I) as defined above for use as a medicament and to the crystalline compound (I) as defined above for use in treating or preventing infectious diseases.

The Advantages of The Crystal A of The Compound (I)

The Crystal A of the compound (I) is not bulky, is very pure and is very stable against heat and light. Therefore, the Crystal A of the compound (I) is suitable for a pharmaceutical product and is easy to handle in pharmaceutical preparations and in storage.

Further, the Crystal A of the compound (I) has sufficient filtration rate and the operation efficiency in case of producing it is very high. Therefore, the Crystal A of the compound (I) is very suitable to produce even in a large scale such as a laboratory scale.

Moreover, due to its ease to be filtered, impurities are difficult to mix in the purification step. Therefore, the compound (I) with high quality can be produced.

As stated above, the Crystal A of the compound (I) possesses very good advantages and is much superior to the amorphous product of the compound (I) known from U.S. patent 4,559,334.

In order to show said advantages of the Crystal A of the compound (I), the comparative test results on stability between the Crystal A of the compound (I) and the compound (I) given by aforesaid U.S. Patent

4,559,334 are shown in the following.

Test Sample

Sampe 1 - the compound (I) obtained in Example 14 of U.S. patent 4,559,334
Sample 2 - the compound (I) obtained in Example 16 of U.S. patent 4,559,334
Sample A - Crystal A of the compound (I) of the present invention

Test Method

The stability of each test sample was examined under the condition of 50 • C in a closed container.

Color of the solution of each sample was determined by measuring transmittance at 510 nm with spectrophotometer (T %) (1 % solution in 1 % $NaHCO_3$ aqueous solution was used).

The potency of each sample was determined by liquid chromatography and the residual percentage to the initial value was calculated.

Test Results

Test Sample	Test Item	Initial	After 1 day	After 7 days
Sample 1	appearance	pale brownish yellow powder	ditto	brownish yellow powder
	color of the solution(T%)	47.0	39.2	25.5
	potency (%)	100	97.2	85.1
Sample 2	appearance	yellow powder	ditto	brownish yellow powder
	color of the solution(T%)	63.8	54.5	37.3
	potency (%)	100	89.3	52.4
Sample A	appearance	yellowish white crystal	ditto	ditto
	color of the solution(T%)	98.9	98.9	98.7
	Potency (%)	100	99.8	99.4

As shown in the test results, there was slight change in the appearance of Samples 1 and 2, while there was no change in the appearance of Sample A.

Further, there was significant lowering of the transmittance (T %) in case of Samples 1 and 2, while there was almost no lowering in case of Sample A.

These results indicated that Samples 1 and 2 were much easier to discolor than Sample A.

Further, as shown in the test results, the potency of Samples 1 and 2 apparently decreased, while the potency of Sample A was almost unchanged.

As stated above, only after 7 days there appeared much difference regarding the stability between the Crystal A of the compound (I) and the compound (I) given by U.S. Patent No. 4,559,334.

Namely, it turned out that the Crystal A of the compound (I) was much superior to the compound (I) given by said U.S. Patent.

The Preparation Of Crystal A Of The Compound (I)

Example 1

To a solution of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(an amorphous product)(0.5 g) in methanol (10 ml) was added dropwise warm water (35 • C; 1.5 ml) at 35 • C and the resultant solution was stirred slowly for 3 minutes, then allowed to stand at room temperature. The resultant crystals were collected by filtration, washed with water and then dried to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) as crystals (Crystal A)(0.4 g).

IR (Nujol®) : 1760, 1670, 1620 cm^{-1}

In the following, powder X-ray diffraction pattern of this Crystal A was shown.

The measurement condition was as follows.

Target : Cu Filter : Ni

Voltage : 30 kv Current: 10 mA

Detector : Scintillation Counter

2θ (°)	relative intensity
11.7	18
12.5	15
14.7	76
16.6	16
17.8	56
18.9	22
19.1	16
21.5	100
22.0	70
23.4	38
24.4	80
25.3	22
26.9	10
27.6	22
28.0	40
29.6	18

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

1. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which shows the peaks at the diffraction angles shown in the following table in its powder X-ray diffraction pattern, the measurement condition being as follows:
   Target: Cu Filter: Ni
   Voltage: 30 kV Current: 10 mA
   Detector: Scintillation Counter

2 θ (°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.4
about 28.0

2. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which is obtainable by dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand.

3. A process for preparing crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which comprises dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand.

4. A pharmaceutical composition containing the crystalline compound of any of claims 1 to 3 as active ingredient in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

5. A use of the compound of any of claims 1 to 3 for manufacture of medicament for treating or preventing infectious diseases.

6. A crystalline compound of any of claims 1 to 3 for use as a medicament.

7. A crystalline compound of any of claims 1 to 3 for use in treating or preventing infectious diseases.

Claims for the following Contracting State : ES

1. A process for preparing crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyimonoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which shows the peaks at the diffraction angles shown in the following table in its powder X-ray diffraction pattern, the measurement condition being as follows:
Target: Cu Filter: Ni
Voltage: 30 kV Current: 10 mA
Detector: Scintillation Counter

2 θ (°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.4
about 28.0

which comprises dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand.

2. A process for preparing crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which comprises dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand.

3. A process for preparing a pharmaceutical composition comprising mixing the crystalline compound of any of claims 1 to 2 as active ingredient with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. A process for preparing a pharmaceutical composition containing crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which comprises dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand, and mixing it as active ingredient with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

5. A process of using the compound of any of claims 1 to 2 for manufacture of medicament for treating or preventing infectious diseases.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

1. Kristalline 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer), die in ihrem Pulver-Röntgenbeugungsdiagramm Peaks aufweist bei den verschiedenen Beugungswinkeln, wie sie in der folgenden Tabelle angegeben sind, wobei die Meßbedingungen die folgenden waren:
   Target: Cu Filter: Ni
   Spannung 30 kV Strom: 10 mA
   Detektor: Szintillations-Zähler

2θ (°)
etwa 14,7
etwa 17,8
etwa 21,5
etwa 22,0
etwa 23,4
etwa 24,4
etwa 28,0

2. Kristalline 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer), die erhältlich ist durch Auflösen von 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) in einem Alkohol, weiteres langsames Rühren der Lösung unter Erwärmen, anschließendes Abkühlen der Lösung auf Raumtemperatur und Stehenlassen der Lösung.

3. Verfahren zur Herstellung der kristallinen 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer), das umfaßt das Auflösen der 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) in einem Alkohol, das weitere langsame Rühren der Lösung unter Erwärmen, das anschließende Abkühlen der Lösung auf Raumtemperatur und das Stehenlassen der Lösung.

4. Pharmazeutische Zusammensetzung, welche die kristalline Verbindung nach einem der Ansprüche 1 bis 3 als aktiven Bestandteil (Wirkstoff) in Kombination (Assoziation) mit einem pharmazeutisch akzeptablen, im wesentlichen nicht-toxischen Träger oder Exzipienten enthält.

5. Verwendung der Verbindung nach einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Behandlung oder Prävention von Infektionserkrankungen.

6. Kristalline Verbindung nach einem der Ansprüche 1 bis 3 für die Verwendung als Arzneimittel.

7. Kristalline Verbindung nach einem der Ansprüche 1 bis 3 für die Verwendung zur Behandlung oder Prävention von Infektionserkrankungen.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von kristalliner 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer), die in ihrem Pulver-Röntgenbeugungsdiagramm Peaks aufweist bei den verschiedenen Beugungswinkeln, wie sie in der folgenden Tabelle angegeben sind, wobei die Meßbedingungen die folgenden waren:
   Target: Cu Filter: Ni
   Spannung 30 kV Strom: 10 mA
   Detektor: Szintillations-Zähler

2θ (°)
etwa 14,7
etwa 17,8
etwa 21,5
etwa 22,0
etwa 23,4
etwa 24,4
etwa 28,0

das umfaßt das Auflösen der 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) in einem Alkohol, das weitere langsame Rühren der Lösung unter Erwärmen, das anschließende Abkühlen der Lösung auf Raumtemperatur und das Stehenlassen der Lösung.

2. Verfahren zur Herstellung der kristallinen 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer), das umfaßt das Auflösen der 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) in einem Alkohol, das weitere langsame Rühren der Lösung unter Erwärmen, das anschließende Abkühlen der Lösung auf Raumtemperatur und das Stehenlassen der Lösung.

3. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das umfaßt das Mischen der kristallinen Verbindung nach einem der Ansprüche 1 bis 2 als aktiven Bestandteil (Wirkstoff) mit einem pharmazeutisch akzeptablen, im wesentlichen nicht-toxischen Träger oder Exzipienten.

4. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, die kristalline 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) enthält, das umfaßt das Auflösen der 7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure (syn-Isomer) in einem Alkohol, das weitere langsame Rühren der Lösung unter Erwärmen, das anschließende Abkühlen der Lösung auf Raumtemperatur und das Stehenlassen der Lösung sowie das Mischen derselben als aktiven Bestandteil (Wirkstoff) mit einem pharmazeutisch akzeptablen, im wesentlichen nicht-toxischen Träger oder Exzipienten.

5. Verfahren zur Verwendung der Verbindung nach einem der Ansprüche 1 bis 2 zur Herstellung eines Arzneimittels zur Behandlung oder Prävention von Infektionserkrankungen.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

1. Acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin qui présente les pics aux angles de diffraction indiqués dans le tableau suivant dans son diagramme de diffraction des rayons X de poudre, les conditions de mesure étant les suivantes :
   Cible : Cu Filtre : Ni
   Tension : 30 kV Intensité du courant : 10 mA
   Détecteur : Scintillomètre

2 θ (°)
environ 14,7
environ 17,8
environ 21,5
environ 22,0
environ 23,4
environ 24,4
environ 28,0

2. Acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin que l'on peut obtenir en dissolvant de l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) dans un alcool, en continuant d'agiter lentement la solution en la chauffant, puis en refroidissant la solution à température ambiante et en laissant reposer la solution.

3. Procédé de préparation d'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin qui comprend les étapes consistant à dissoudre l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) dans un alcool, à continuer d'agiter lentement la solution en la chauffant, puis à refroidir la solution à température ambiante et à laisser reposer la solution.

4. Composition pharmaceutique contenant le composé cristallin selon l'une quelconque des revendications 1 à 3 comme constituant actif en association avec un véhicule ou un excipient pharmaceutiquement acceptable, essentiellement non toxique.

5. Emploi du composé selon l'une quelconque des revendications 1 à 3 pour la fabrication d'un médicament pour le traitement ou la prévention de maladies infectieuses.

6. Composé cristallin selon l'une quelconque des revendications 1 à 3 destiné à être utilisé comme médicament.

7. Composé cristallin selon l'une quelconque des revendications 1 à 3 destiné à être utilisé dans le traitement ou la prévention de maladies infectieuses.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin qui présente les pics aux angles de diffraction indiqués dans le tableau suivant dans son diagramme de diffraction des rayons X de poudre, les conditions de mesure étant les suivantes :
   Cible : Cu Filtre : Ni
   Tension : 30 kV Intensité du courant : 10 mA

Détecteur : Scintillomètre

2 θ (°)
environ 14,7
environ 17,8
environ 21,5
environ 22,0
environ 23,4
environ 24,4
environ 28,0

qui comprend les étapes consistant à dissoudre l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) dans un alcool, à continuer d'agiter lentement la solution en la chauffant, puis de refroidir la solution à température ambiante et de laisser la solution reposer.

2. Procédé de préparation d'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin qui comprend les étapes consistant à dissoudre l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vi nyl-3-céphème-4-carboxylique (isomère syn) dans un alcool, à continuer d'agiter lentement la solution en la chauffant, puis à refroidir la solution à température ambiante et à laisser reposer la solution.

3. Procédé de préparation d'une composition pharmaceutique comprenant le mélange du composé cristallin selon l'une quelconque des revendications 1 à 2, comme constituant actif, avec un véhicule ou un excipient pharmaceutiquement acceptable, essentiellement non toxique.

4. Procédé de préparation d'une composition pharmaceutique contenant de l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) cristallin qui comprend les étapes consistant à dissoudre l'acide 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique (isomère syn) dans un alcool, à continuer d'agiter lentement la solution en la chauffant, puis à refroidir la solution jusqu'à la température ambiante et à laisser la solution reposer, et à la mélanger comme constituant actif, avec un véhicule ou un excipient pharmaceutiquement acceptable, essentiellement non toxique.

5. Procédé d'utilisation du composé selon l'une quelconque des revendications 1 à 2 pour la fabrication d'un médicament pour le traitement ou la prévention de maladies infectieuses.

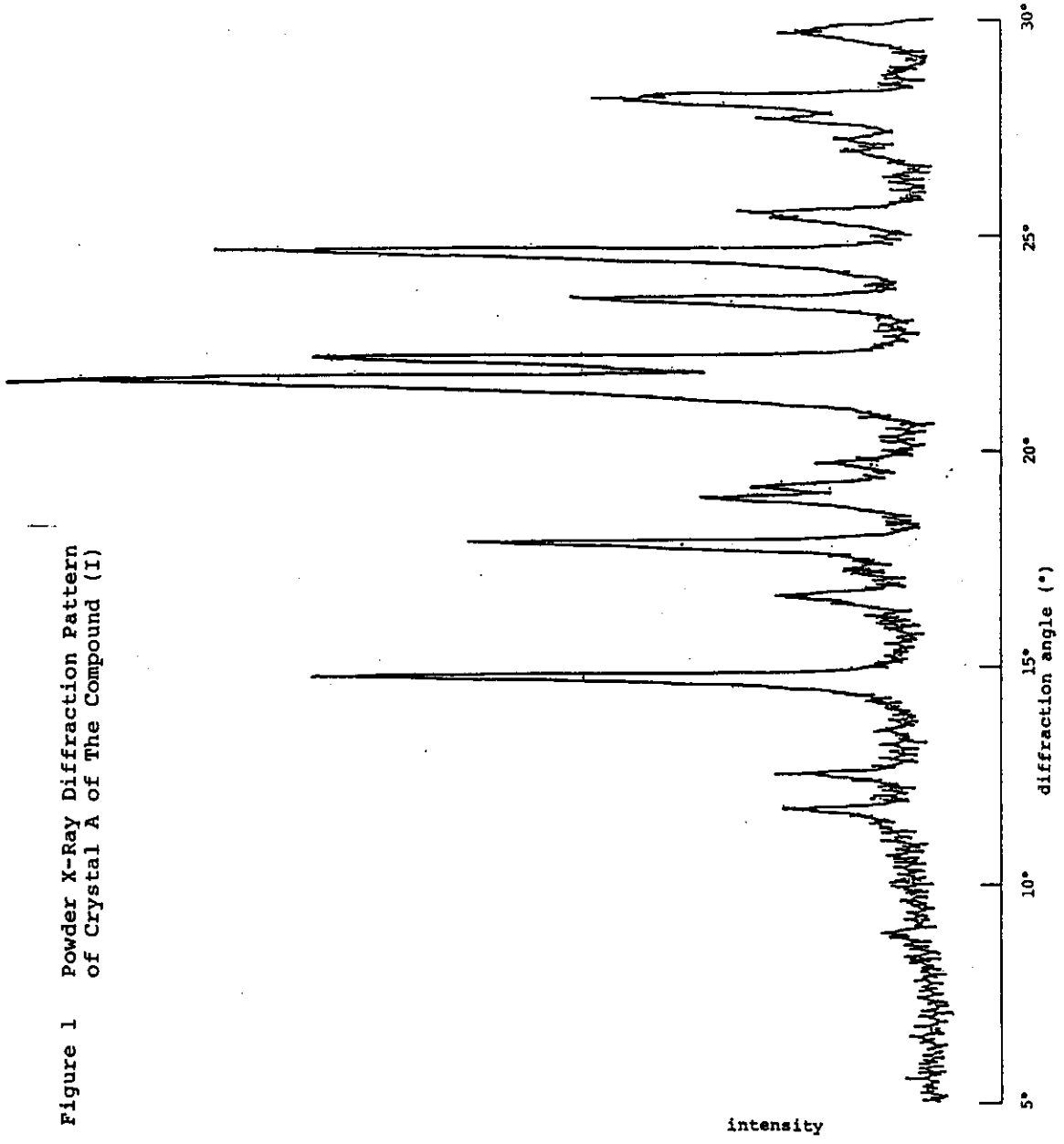


Figure 1 Powder X-Ray Diffraction Pattern of Crystal A of The Compound (I)

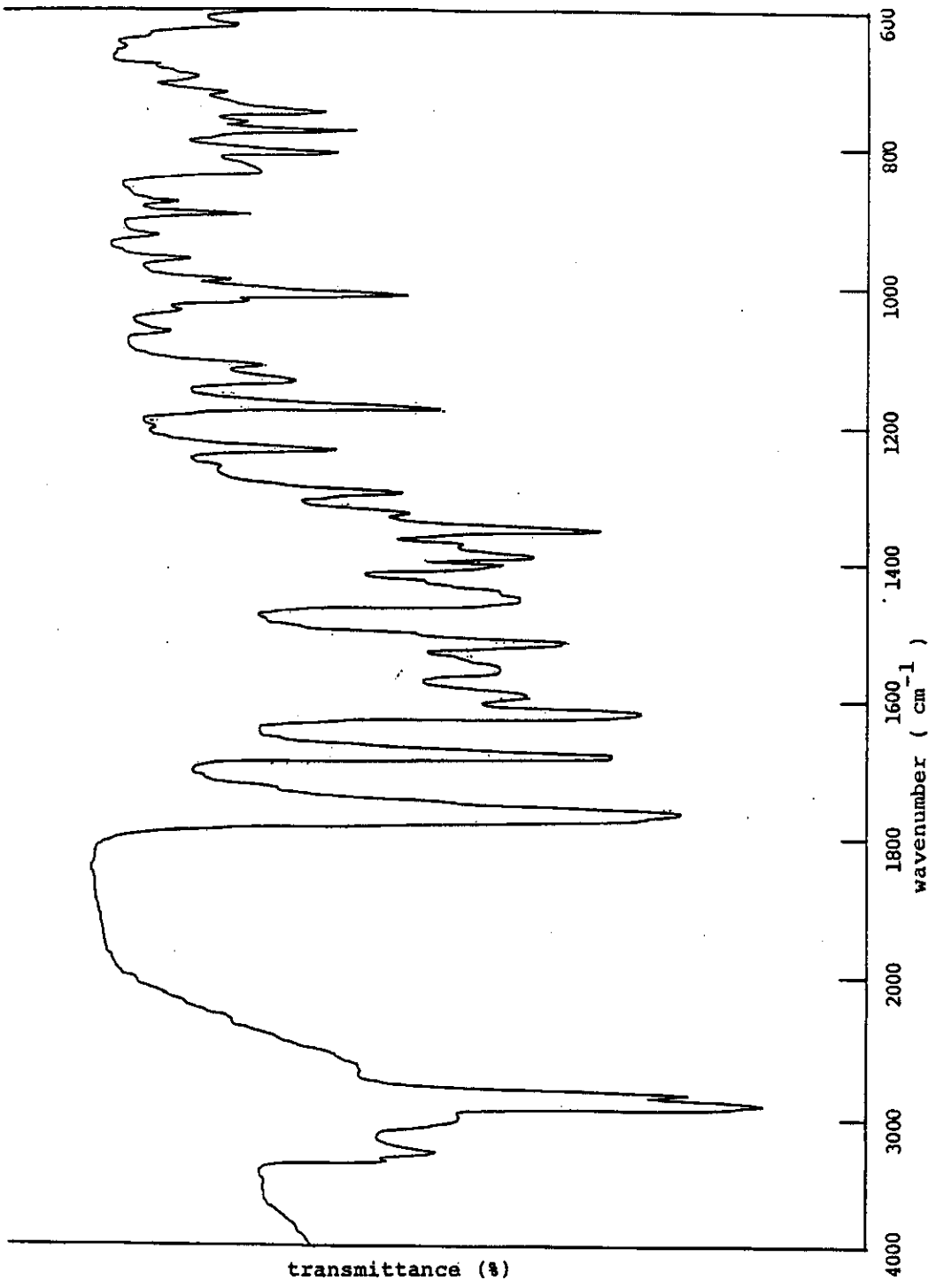


Figure 2 Infrared Absorption Spectrum of Crystal A of The Compound (I)

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Title NOVEL CRYSTALLINE
7-(2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO)-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER).

Applicant/Proprietor
FUJISAWA PHARMACEUTICAL CO., LTD., 3, Doshomachi 4-chome Higashi-ku, Osaka-shi Osaka 541, Japan [ADP No. 50507631001]

Inventors
TAKAO TAKAYA, 5-87, Suimeidai 1-chome, Kawanishi-shi Hyogo 666-01, Japan [ADP No. 56350820001]

FUMIYUKI SHIRAI, 2-10, Midorigaoka 2-chome, Ikeda-shi Osaka 563, Japan [ADP No. 56350838001]

HITOSHI NAKAMURA, 244-1, Aogein, Mino-shi Osaka 562, Japan [ADP No. 56350846001]

YASUNOBU INABA, 2-6-504, Kitamidorigaoka 1-chome, Toyonaka-shi Osaka 560, Japan [ADP No. 56350853001]

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Address for Service
STEVENS, HEWLETT & PERKINS, 1 St Augustine's Place, BRISTOL, BS1 4UD, United Kingdom [ADP No. 00001545002]

EPO Representative
DR. RER. NAT. DIETMAR TÜRK, Türk, Gille + Hrabal Patentanwälte Bruckner Strasse 20, D-4000 Düsseldorf 13, Federal Republic of Germany [ADP No. 50034693001]

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DR. RER. NAT. DIETMAR TÜRK, Türk, Gille + Hrabal Patentanwälte
Bruckner Strasse 20, D-4000 Düsseldorf 13, Federal Republic of
Germany [ADP No. 50034693001]
to
DR. RER. NAT. DIETMAR TÜRK, Türk, Gille, Hrabal, Leifert
Patentanwälte Brucknerstrasse 20, D-40593 Düsseldorf, Federal
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FUJISAWA PHARMACEUTICAL CO., LTD., 3, Doshomachi 4-chome Higashi-ku, Osaka-shi Osaka 541, Japan

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