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CA 2615418 C 2011/04/26

(11)(21) 2 615 418

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2006/05/12
(87) Date publication PCT/PCT Publication Date: 2007/02/15
(45) Date de délivrance/Issue Date: 2011/04/26
(85) Entrée phase nationale/National Entry: 2008/01/15
(86) N° demande PCT/PCT Application No.: EP 2006/004473
(87) N° publication PCT/PCT Publication No.: 2007/016982
(30) Priorité/Priority: 2005/07/28 (AR P20050103131)

(51) Cl.Int./Int.Cl. *C07F 9/6506* (2006.01), *A61K 31/675* (2006.01), *C07F 9/38* (2006.01)

(72) Inventeurs/Inventors:
LABRIOLA, RAFAEL ALBERTO, AR;
TOMBARI, DORA GRACIELA, AR;
VECCHIOLI, ADRIANA, AR

(73) Propriétaire/Owner:
GADOR S.A., AR

(74) Agent: SHAPIRO COHEN

(54) Titre : FORME CRISTALLINE DE L'ACIDE ZOLEDRONIQUE, SON PROCEDE D'OBTENTION ET COMPOSITION PHARMACEUTIQUE LA RENFERMANT

(54) Title: A CRYSTALLINE FORM OF THE ZOLEDRONIC ACID, A PROCESS TO OBTAIN IT AND THE PHARMACEUTICAL COMPOSITION COMPRISING IT

(57) Abrégé/Abstract:
This invention refers to a new crystalline form of the Zoledronic acid, characterized by its X-rays diffractogram as well as by its spatial atomic distribution in the red crystalline and its curves of thermal analysis. There is also included a method to obtain this crystalline form, which includes the synthesis of the corresponding acid and the pharmaceutical composition this crystalline form comprises.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2007 (15.02.2007)

PCT

(10) International Publication Number
WO 2007/016982 A1

(51) International Patent Classification:
C07F 9/6506 (2006.01) *A61K 31/675* (2006.01)
C07F 9/38 (2006.01)

(21) International Application Number:
PCT/EP2006/004473

(22) International Filing Date: 12 May 2006 (12.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20050103131 28 July 2005 (28.07.2005) AR

(71) Applicant *(for all designated States except US)*: **GADOR S.A.** [AR/AR]; Darwin 429, 1414 Buenos Aires (AR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LABRIOLA, Rafael, Alberto** [AR/AR]; c/o Darwin 429, 1414 Buenos Aires (AR). **TOMBARI, Dora, Graciela** [AR/AR]; c/o Darwin 429, 1414 Buenos Aires (AR). **VECCHIOLI, Adriana** [IT/AR]; c/o Darwin 429, 1414 Buenos Aires (AR).

(74) Agents: **WINKLER, Andreas** et al.; Boehmert & Boehmert, Hollerallee 32, 28209 Bremen (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/016982 A1

(54) Title: A CRYSTALLINE FORM OF THE ZOLEDRONIC ACID, A PROCESS TO OBTAIN IT AND THE PHARMACEUTICAL COMPOSITION COMPRISING IT

(57) Abstract: This invention refers to a new crystalline form of the Zoledronic acid, characterized by its X-rays diffractogram as well as by its spatial atomic distribution in the red crystalline and its curves of thermal analysis. There is also included a method to obtain this crystalline form, which includes the synthesis of the corresponding acid and the pharmaceutical composition this crystalline form comprises.

"A crystalline form of the Zoledronic acid, a process to obtain it and the pharmaceutical composition comprising it"

Field of the invention

This invention refers to a new crystalline form of zoledronic acid, characterized by its diffractogram of X-rays as well as by its special atomic distribution in the crystalline network and its thermal analysis curves.

There is also included a method to obtain this crystalline form, which comprises the synthesis of the corresponding acid and the pharmaceutical composition comprised by this crystalline form.

Background of the Invention

Zoledronic acid (I) is a bisphosphonic acid, which acts as an inhibitor of the bone osteoclastic resorption. This compound, chemically called 1-hydroxy-2-(imidazol-1-yl)ethydilene bisphosphonic acid, is sold in the USA under the trade name of Zometa® (zoledronic acid for injectables).

Zoledronic acid belongs to the family of the bisphosphonates well known for its features useful when treating diseases caused by dysfunctions in the metabolism of calcium and phosphorous [see for example K. R. Williams – J. Chem. Ed. 81, 1406 (2004)].

There exist several patents describing methods for the obtention of bisphosphonates, particularly for zoledronic acid and its salts DE 3626058 (1988); US 4777163 (1988); EP 258618 (1988); US 4939130 (1990) may be mentioned.

In Chemical Abstracts there are registered various forms of free zoledronic acid and its salts :

1. Anhydrous Zoledronic acid (RN: 118072-93-8).
2. Monohydrate Zoledronic acid (RN: 165800-06-6).
3. Zoledronic Acid, anhydrous disodium salt (RN: 131654-46-1).
4. Zoledronic Acid, monohydrate disodium salt (RN: 165800-07-7)
5. Zoledronic Acid, monohydrate trisodium salt (RN: 165800-08-8).
6. Zoledronic Acid, magnesium salt (RN: 157432-59-2).
7. Zoledronic Acid, zinc salt (RN: 157432-58-1).

US Patent No. 4939130 describes that the zoledronic acid obtained has a melting point of 239 °C.

Particularly, in the request of patent US Serial No. 2005/0054616 diverse crystalline forms are described for the free acid and its sodium salts.

Seven crystalline forms are described in this document for zoledronic acid, identified as forms I, II, XII, XV, XVIII, XX and XXVI through their diffractograms of X-rays and TGA (Thermogravimetric Analysis).

The use of methansulphonic acid as a solvent in the preparation of alendronic acid and its salts is described in US Patent No. 4922007 (1990) and EP 462663 (1991).

Summary of the Invention

This invention refers to a new polymorphic form of zoledronic acid, which exists in form of trihydrate and to a method of obtaining it.

According to one aspect of the present invention, there is provided a procedure to prepare a crystalline form of hydrated zoledronic acid according to the invention, characterized in that it comprises the following steps:

a. reacting 1- imidazol-1-yl acetic acid with phosphorous trichloride and water, using methanesulphonic acid as a solvent;
b. hydrolyzing, by adding water and heating, the intermediate substances generated in the reaction;
c. precipitating the raw acid of the reaction means, through partial neutralization and cooling;
d. dissolving the raw zoledronic acid in hot water;
e. adding this concentrate into refrigerated water, so that the crystallization occurs within the desired temperature scope;
f. once the crystallization is completed, cooling down, filtering the precipitate and washing it with water; and
g. drying the end product.

According to another aspect of the present invention, there is provided a procedure characterized in that the molar ratio in step a. of phosphorous trichloride: 1- imidazol-l-yl acetic acid is comprised between 3:1 to 8:1.

According to another aspect of the present invention, there is provided a procedure characterized in that the molar ratio in step a. of phosphorous trichloride: water is comprised between 0.8:1 to 1.2:1.

According to another aspect of the present invention, there is provided a procedure characterized in that the hydrolysis in step b. is conducted at a temperature between 80 and 125 °C, during at least half an hour.

According to another aspect of the present invention, there is provided a procedure characterized in that the dissolution temperature of the step d. is comprised between 50 and 105 °C.

According to another aspect of the present invention, there is provided a procedure according to claim 16 characterized in that the dissolution temperature is comprised between 80 and 100 °C.

The existence of a new crystalline stable form and of a simple and reproducible method for obtaining it widens the spectrum of possibilities for the design of new pharmaceutical forms.

The use of the methansulfonic acid as a solvent to prepare zoledronic acid results in a homogeneous reaction.

In other preparations where a diluent is used [see for instance US 4777163 (1988) example 1; US 2005/0054616 (2005) examples 1 - 8], the reaction occurs in a heterogeneous stage.

The use of the said methansulphonic acid for obtaining zoledronic acid is described in the literature [G. R. Kieczykowski et al. - J. Org. Chem. 60, 8310 (1995)], nevertheless the output obtained in that publication, being of 31 %, discourages its use at an industrial scale and has not been protected by patents.

In our case, the use of water as a reactant, the absence of adding phosphorous acid and the molar ratios of reactants and of solvent used, result in significant differences as regards the descriptive procedure giving rise to a substantial increase in the output up to a value of 83% which turns this process economically apt for the manufacture of zoledronic acid.

Brief Description of the Drawings

Figure I shows the X-rays dust diffractogram of this new crystalline form.

Figure II corresponds to the curves obtained through the TGA analysis

(Thermogravimetric Analysis) and DSC (Differential Scanning Calorimetry) of this new crystalline form.

Figure III corresponds to the infrared spectrum of this new crystalline form.

Figure IV corresponds to the spatial disposition of the atoms in the unitary cell of this new crystalline form.

Detailed Description of the Invention

The X-rays diffraction analysis and the thermal analysis (TGA, DSC) were carried out at the Atomic Energy National Commission- Condensed Matter Group.

The equipment used is a Philips model X'Pert with a PW3710 unit to obtain the diffractograms of the samples.

A K-Alpha wavelength of 1.54060 A was used.

The water losses were determined through the TGA (Thermogravimetric Analysis) with a Shimadzu DTG-50 equipment with a 40 ml/min dry air flow.

The melting points result from the curves obtained through DSC (Differential Scanning Calorimetry) in a Shimadzu DSC-60 equipment at 10 °C/min with a 30 ml/min nitrogen flow.

The infrared spectrums were carried out in a Shimadzu FTIR-8100 equipment, using a solid substance in the form of pills with KBr.

The new crystalline form corresponds to a trihydrate, its study by means of X rays of a crystal shows that the distribution of its atoms in the crystalline network corresponds to the special group P-1, characterized by the following cell parameters (A): a: 6.874; b: 9.450; c: 10.825; a: 65.14 °; (3: 76.83 °;y: 81.39 °.

In order to compare, the theoretical X-rays diffractogram for the trihydrate form (Figure I A), the dust X-rays diffractogram obtained with the form I (monohydrate) (Figure I B) and the atoms spatial distribution in the unitary cell of the crystalline network for the monohydrate form (Figure IV A) are also shown.

The trihydrate crystalline form described in this document, by means of the exposition in an environment with 75 to 96 % relative humidity at 30 - 40 °C during 24 hours, does not absorb water and maintains its X-rays dust diffractogram and its thermal profile is (TGA and DSC) unchanged.

The existence of three water molecules for each one of zoledronic acid may be clearly seen in Figure IV.

This new crystalline form of this invention is characterized for presenting in its X rays dust diffractogram peaks in angles of 20 of 9.2; 10.4; 14.7; 16.4 ° ± 0.2°.

It is also characterized because its thermal analysis (TGA and DSC) show an endothermy between 68 - 128 °C associated to a loss of mass of around 16 - 17 %, which corresponds to a trihydrate and a melting endothermy followed by decomposition at around 211-215°C.

This new trihydrate form has always been obtained in our laboratory without difficulties and in a reproducible way.

Zoledronic acid was prepared by a method not described for this substance and advantageous because of the output and the raw product's quality obtained.

The same consists of reacting 1- imidazol-1-yl acetic acid with phosphorous trichloride and water, in the presence of methanesulphonic acid.

The suspension is heated at 60 - 65 °C over 10 - 15 hours, preferably between 9 - 12 hours, whereupon it turns into a viscous solution.

During all the reaction, there is plenty release of hydrogen chloride.

Once the mass is dissolved by additional addition of water at 8 - 12 °C, it is heated at reflux at 105 - 112 °C over 3 - 5 hours.

It is then partially neutralized with aqueous solution of sodium hydroxide up to a pH between 0 and 0.9, preferably between 0 and 0.4 at a temperature between 20 and 40 °C and the crystallization starts.

It is then cooled down to 0 - 5 °C, filtered, washed by resuspension first in water and then in methanol.

The raw zoledronic acid may be obtained by means of drying at 50 – 80 °C with an output exceeding 80 % and a quality apt for the generation of the crystalline trihydrate form.

To obtain the crystalline trihydrate form of this invention an aqueous hot solution of zoledronic acid, which concentration varies between 1.5 and 10 % (w/v), preferably between 2 and 4% (w/v), is crystallized at a temperature between 5 and 35 °C, preferably between 15 and 25 °C.

In order to achieve this without the need of using large dilutions, the hot solution is poured over a small amount of water, kept at the wanted crystallization temperature.

In this way, the crystallization temperature may be adjusted regulating the volume of the hot solution's aggregate and of the refrigerating liquid's flow.

In this way the new crystalline trihydrate form is obtained, which dust X-rays diffraction spectrum present peaks in values of 2θ of 9.2; 10.4; 14.7; 16.4 ° ± 0.2°.

and which diffractogram corresponds to the one of Figure I.

This substance presents the following physicochemical characteristics.

- The curve corresponding to the TGA (Thermogravimetric Analysis) is shown in Figure II, in which a loss of mass is seen, corresponding to a loss of water, of 16 - 17 %, which corresponds to a trihydrate.
- The curve corresponding to the analysis by DSC (Differential Scanning Calorimetry), observed in Figure III, shows an endothermy at 211 - 215 °C which corresponds to the melting process.

Examples

Merely for illustration purposes, not limiting to the scope of this invention, the following preparation examples are included:

Example 1 – Zoledronic Acid

A suspension of 1-imidazol-1-yl acetic acid (200 g) in methanesulfonic acid 98-99 % (240 ml) is added slowly and blending phosphorous trichloride (856 ml).

The temperature is increased until reaching 55 °C, reflux is observed.

Once the phosphorous trichloride aggregate is finished, the aggregate of water (171 ml) is started, thus increasing the exothermy, which is evidenced through a larger volume of reflux.

During the reaction hydrogen chloride is released.

The mass in suspension slowly dissolves and the solution turns very viscous, thus making the agitation difficult.

After 12 hours reaction at 55-70 °C, water is slowly added (805 ml), in a period of 2-3 hours at a temperature between 8 and 25 °C, with which a fluid solution is achieved.

It is then heated at 105 – 112 °C over 3 hours and the solution is filtered to eliminate impurities.

The resulting solution is partially neutralized at a temperature of 30 – 40 °C with a sodium hydroxide aqueous solution 50 % (w/v) until obtaining a pH of 0.25 ± 0.03

It is then cooled down to 0-5 °C, maintaining this temperature over at least 2 hours the precipitate being filtered.

The same is washed by resuspension once in water (500 ml) and twice in methanol (500 ml each time).

The precipitate may be dried in a stove at 50 - 60 °C, thus obtaining the raw zoledronic acid with a potentiometric titre equal to or exceeding 98 %.

It may also be used humid to prepare the trihydrate form.

The output is 83 %.

Example 2 – Zoledronic Acid Trihydrate

The raw humid zoledronic acid (equivalent to 30 g dry product), obtained in Example 1, is suspended in water (900 ml).

The suspension is heated at reflux, thus obtaining a solution.

This hot solution is slowly added and blended to a refrigerated container, containing water (50 ml).

The inside temperature is adjusted by means of the flow of the refrigerant fluid and the volume of aggregate of the hot concentrated solution, in order to keep it between 15 and 25 °C.

The aggregate requires around 3½ hours.

Once all the zoledronic acid solution is added, it is cooled down to 0 – 5 °C maintaining this temperature over 2 – 3 hours, it is filtered, washed with ice water (30 ml) and dried with air flow at 50 - 60 °C.

The obtained product presents the following physicochemical characteristics.

Diffraction by X-rays (dust method)

It presents peaks in at following values of 2θ 9.2; 10.4; 14.7; 16.4 ° ± 0.2°.

The diffractogram is the one shown in Figure I.

Titre (potentiometric): 99 %

Humidity (Loss by dissection): 16.6 %

TGA (Thermogravimetric Analysis):

The obtained curve is shown in Figure II.

DSC (Differential Scanning Calorimetry)

The obtained curve is shown in Figure II.

Infrared Spectrum (KBr)

Absorption at 3578-3011; 1643.6; 1579.9; 1549.1; 1443.0; 1414.0; 1387.0; 1294.4; 1155.5; 966.5 cm^{-1}

Corresponds to Figure III.

Example 3 – Zoledronic Acid Monohydrate

The raw humid zoledronic acid (equivalent to 90.3 g raw product), obtained according to Example 1, is suspended in water (3050 ml).

The suspension is heated at reflux, with agitation.

Water is added up to a total volume of 3750 ml, by which a total dissolution is obtained.

The heating is then interrupted and the agitation, allowing it to slowly cool down to ambient temperature.

Once the inside temperature is around 70 – 80 °C a frank crystallization starts.

Once the ambient temperature is reached, it is cooled down to 2 – 5 °C, maintained at that temperature during 1½ hours, filtered and the precipitate is washed with ice water.

It is dried in a stove with air flow at 5°C - 60 °C.

169.3 g (89 %) colorless crystals are obtained.

The loss through dissection (6.8%) confirms that this is a monohydrate.

This substance, by diffraction with X-rays, dust method, presents peaks at the following values of 2θ 12.1; 12.8; 15.7; 18.9 ± 0.2, coincident with those described for the form I (US 2005/0054616).

Figure I A shows its diffractogram of dust X-rays and figure IV A the lay-out of the atoms in the unitary cell of the crystalline network for this form.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A crystalline trihydrate form of zoledronic acid.

2. The crystalline trihydrate form of claim 1, wherein its diffractogram of dust X- rays presents peaks at the following values of 2θ: 9.2; 10.4; 14.7; 16.4 ± 0.2.

3. A process to prepare a crystalline form of hydrated zolendronic acid according to claim 1 or 2, by dissolving raw zolendronic acid in hot water and adding this concentrate into refrigerated water in order to achieve a crystallization temperature between 5 and 35°C.

4. The process according to claim 3, wherein the crystallization temperature is between 15 and 25°C.

5. The process according to claim 3 or 4, wherein the following steps are conducted to obtain the raw zolendronic acid:

   a. reacting 1- imidazol-1-yl acetic acid with phosphorous trichloride and water, using methanesulphonic acid as a solvent;
   b. hydrolyzing, by adding water and heating, intermediate substances generated in the reaction; and
   c. precipitating the raw acid of the reaction means, through partial neutralization and cooling.

6. The process according to claim 5, wherein a molar ratio in step a. of phosphorous tri chloride: 1- imidazol-1-yl acetic acid is comprised between 3:1 to 8:1.

7. The process according to claim 5, wherein a molar ratio in step a. of phosphorous trichloride: water is comprised between 0.8:1 to 1.2:1.

8. The process according to claim 5, wherein the hydrolysis in step b. is conducted at a temperature between 80 and 125 °C, during at least half an hour.

9. The process according to claim 5, wherein, the partial neutralization of step c. is conducted by means of an aqueous solution of hydroxides or carbonates of alkaline metals.

10. The process according to claim 9, wherein, in the partial neutralization, the solution is adjusted to a pH comprised between 0 and 0.9.

11. The process according to claim 9, wherein, in the partial neutralization, the solution is adjusted to a pH comprised between 0 and 0.4.

12. The process according to claim 3, wherein the concentration of the zoledronic acid in the hot solution is between 1 and 3.5 % (w/v).

13. The process according to claim 3, wherein a temperature of the hot water for dissolving the raw zolendronic acid is between 50 and 105 °C.

14. The process according to claim 3, wherein a temperature of the hot water for solving the raw zolendronic acid is between 80 and 100 °C.

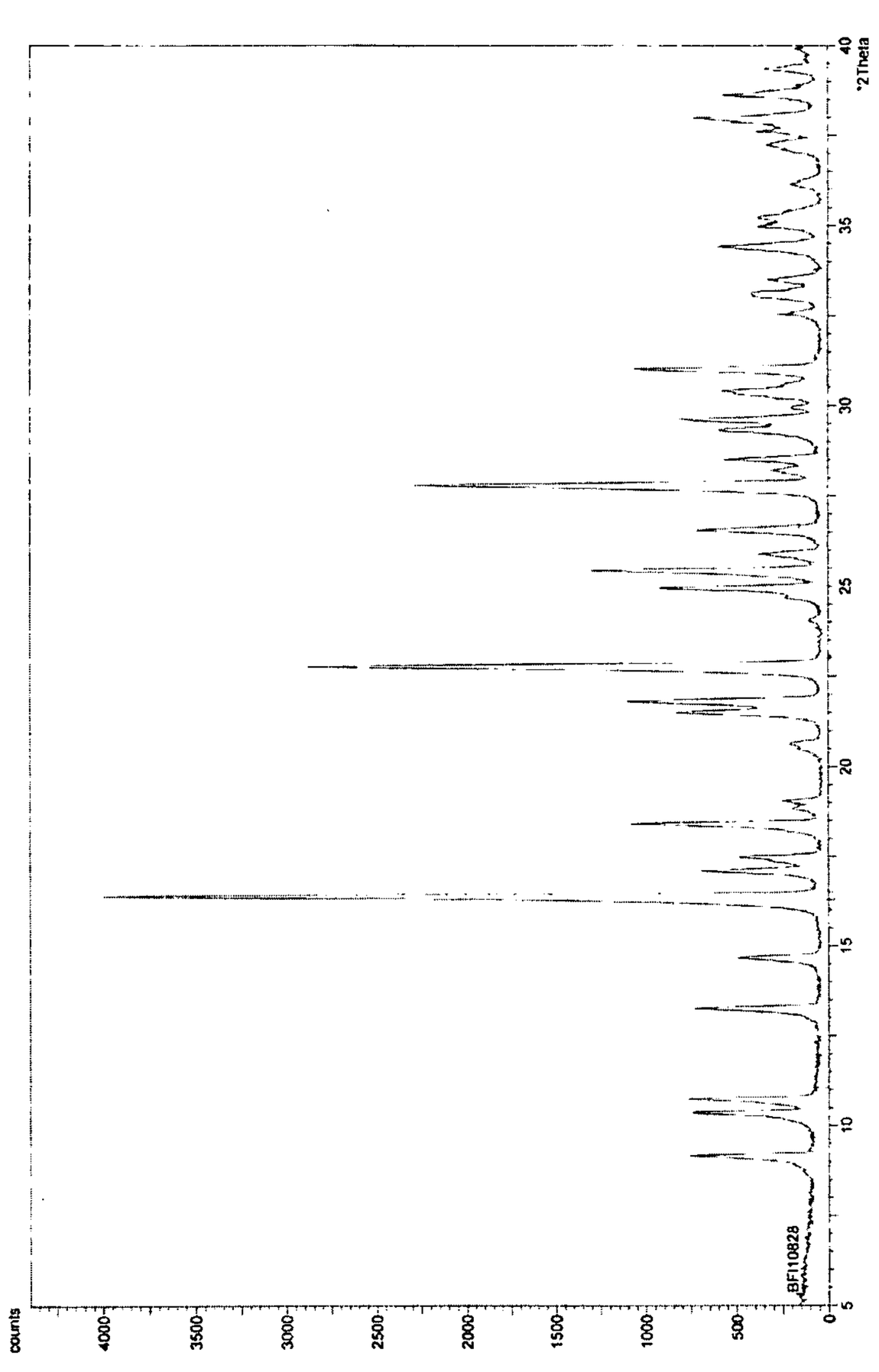
15. The process according to any one of claims 3 to 14, wherein, once the crystallization is completed, the following steps are conducted: cooling down, filtering the precipitate, washing it with water and drying the end product at atmospheric pressure.

16. The process according to claim 15, wherein the drying of the end product is made at the atmospheric pressure and at a temperature between 20 and 80 °C.

17. The process according to claim 15, wherein the drying of the end product is made at the atmospheric pressure and at a temperature between 30 and 60 °C.

18. A Pharmaceutical composition comprising, as the active ingredient, the crystalline tri-hydrate form of zoledronic acid as defined in claim 1 or 2, together with one or more pharmaceutically acceptable vehicles.

Figure I



Zoledronic Acid trihydrate

Diffractogram of dust X-Rays

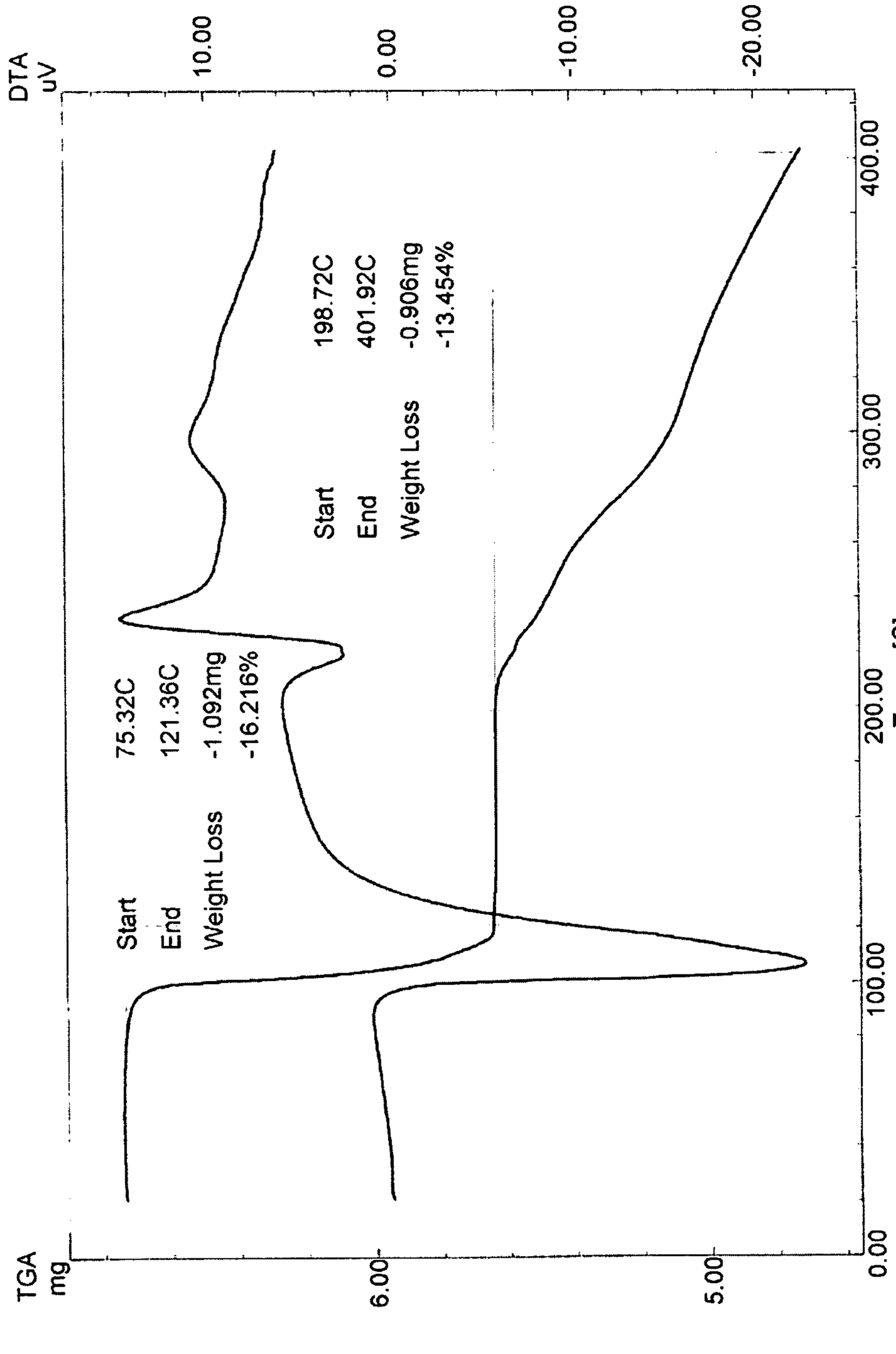


Figure II

Zoledronic acid trihydrate

TGA and DSC

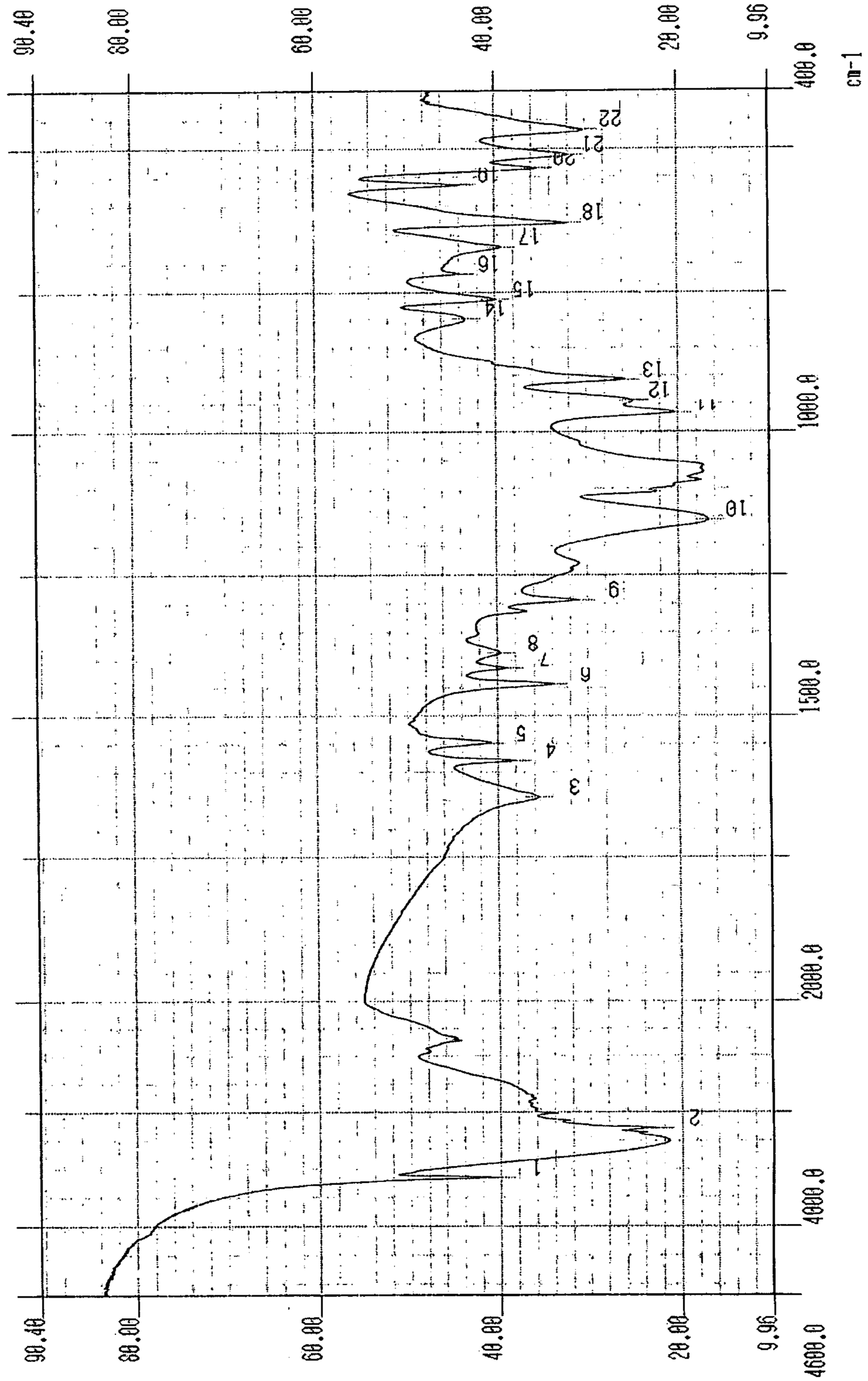


Figure III

Zoledronic acid trihydrate

Infrared Spectrum

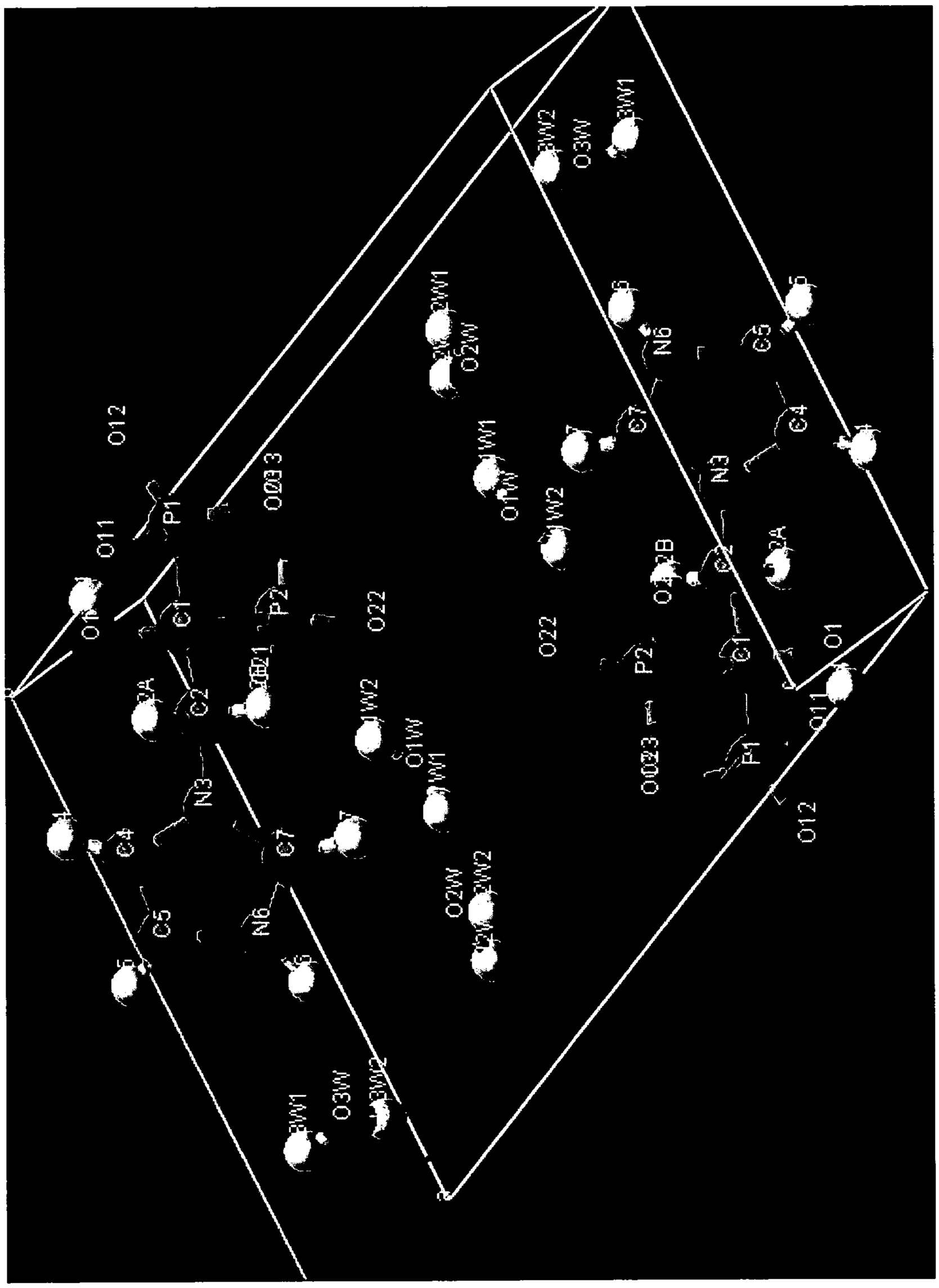


Figure IV

Zoledronic acid trihydrate

Spatial lay-out in the unitary cell

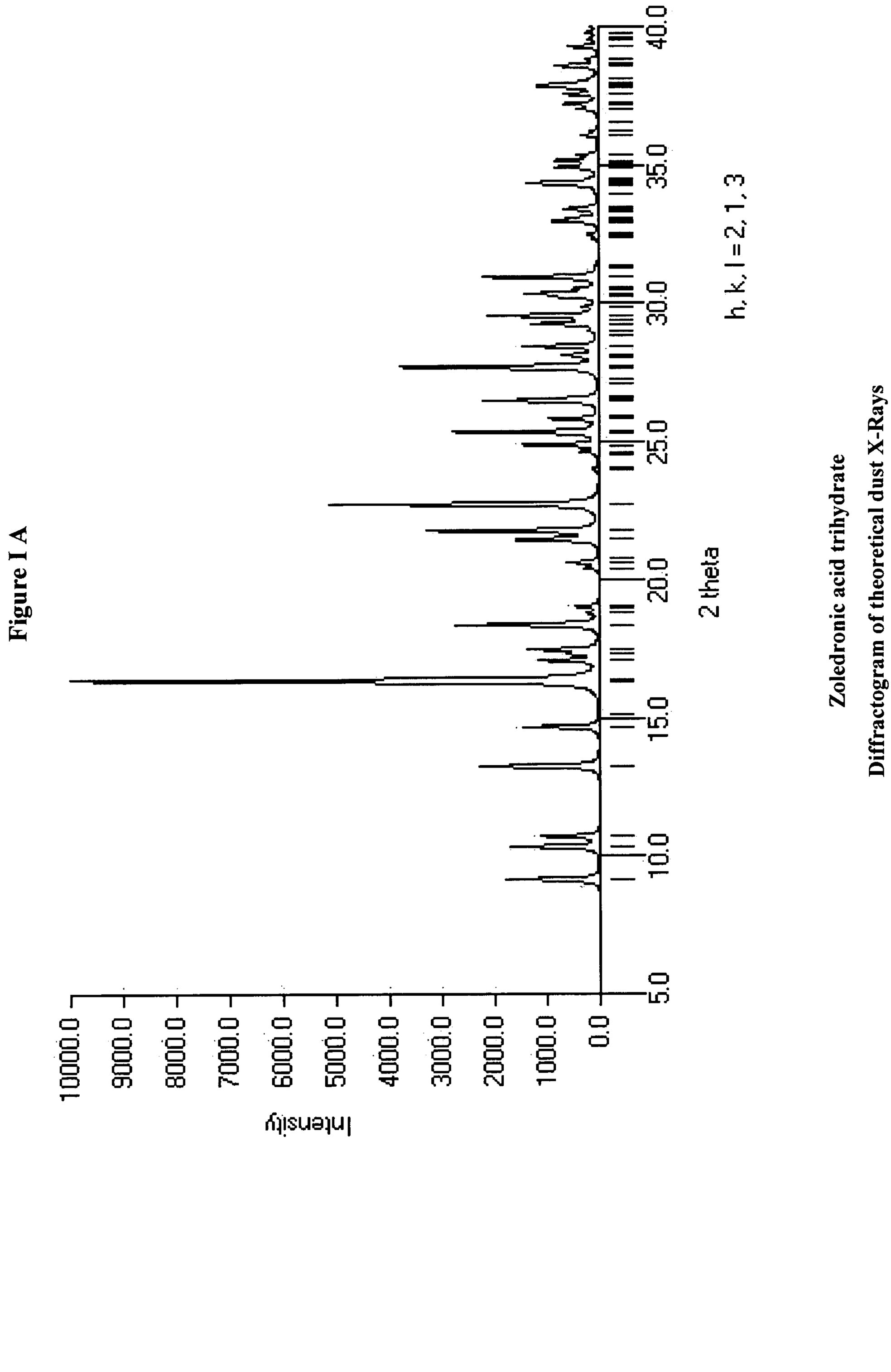
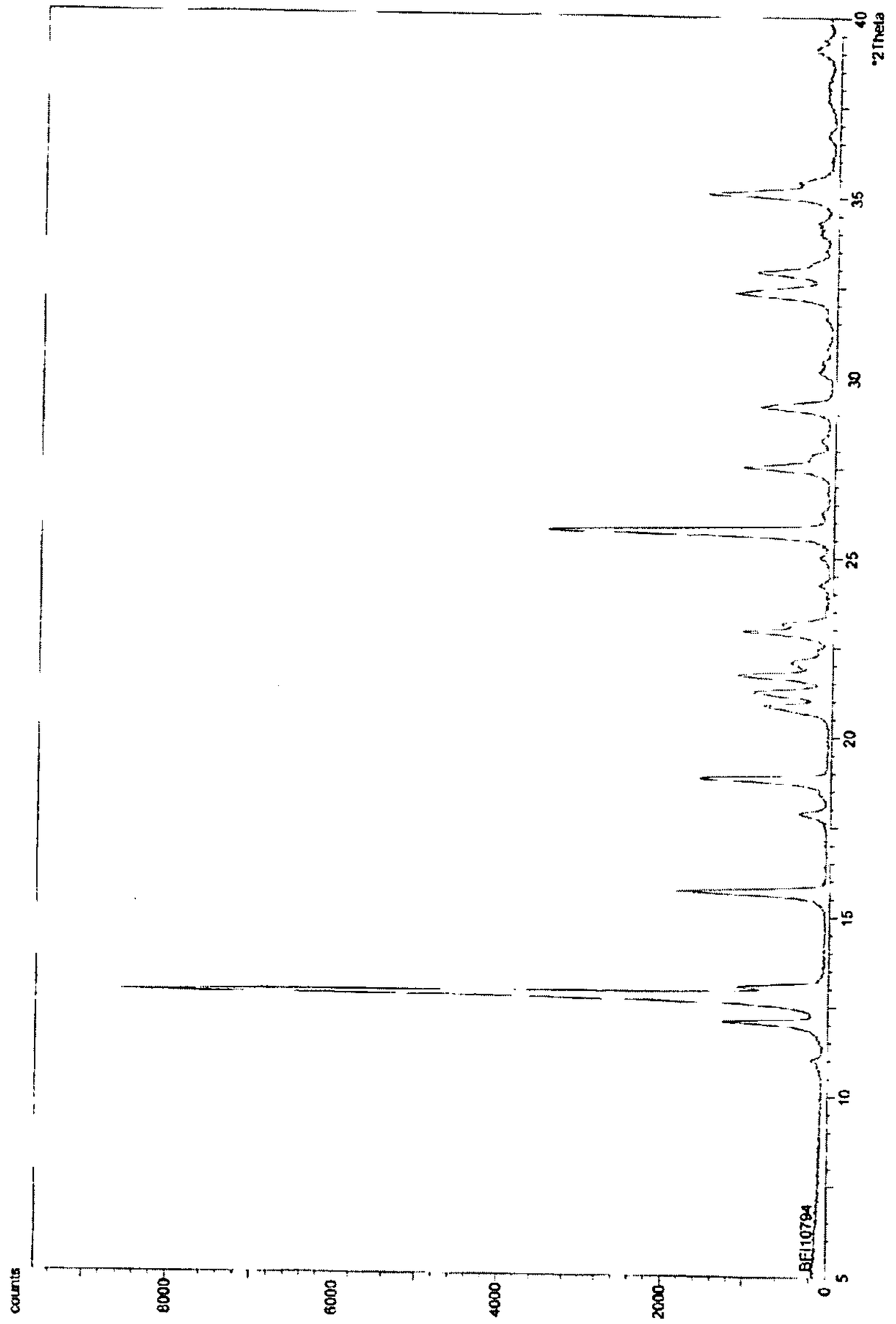


Figure I A

Zoledronic acid trihydrate

Diffractogram of theoretical dust X-Rays

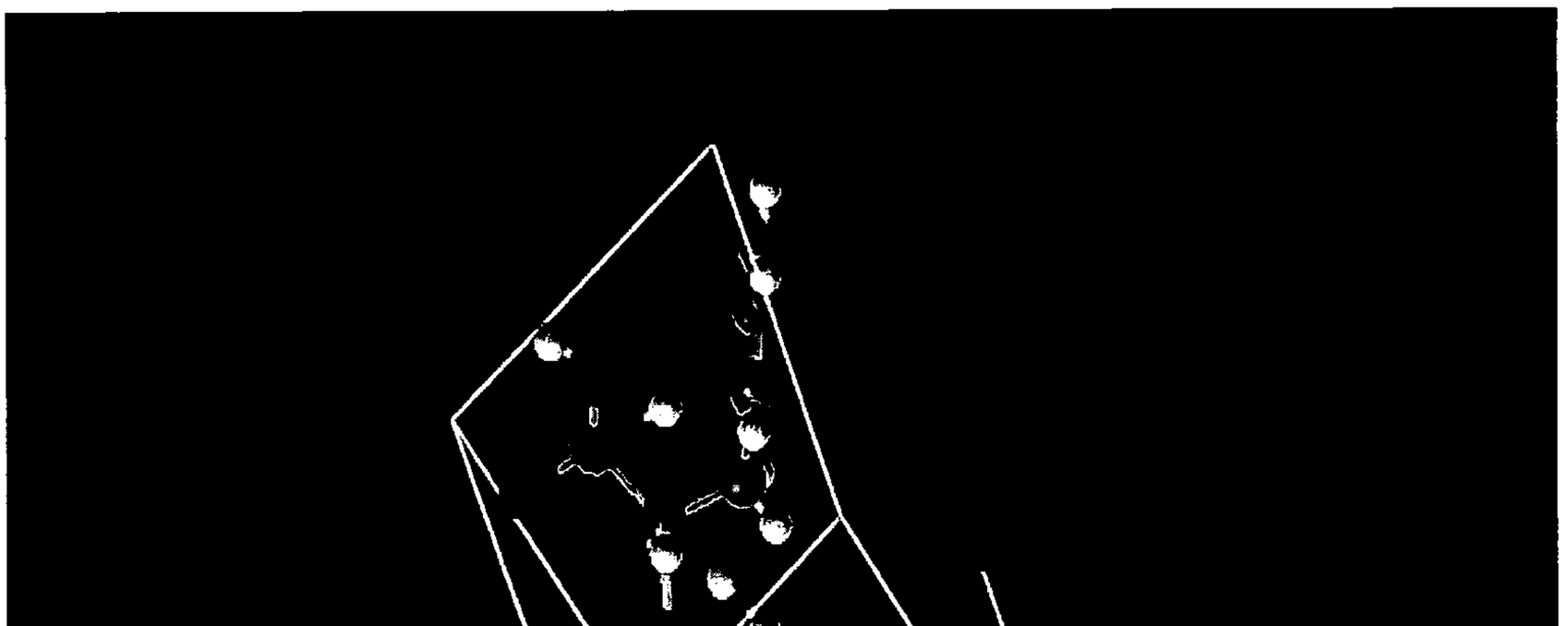
Figure I B



Zoledronic acid monohydrate

Diffractogram of dust X-Rays

Figure IV A



Zoledronic acid monohydrate

Spatial lay-out in the unitary cell