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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
27 March 2008 (27.03.2008)

(10) International Publication Number
WO 2008/035153 A2

(51) International Patent Classiflcation: Not classified

(21) International Application Number:
PCT/IB2007/002192

(22) International Filing Date: 31 July 2007 (31.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1369/CHE/2006 2 August 2006 (02.08.2006) IN
1779/CHE/2006 27 September 2006 (27.09.2006) IN

(71) Applicant *(for all designated States except US):* **ORCHID CHEMICALS & PHARMACEUTICALS LIMITED** [IN/IN]; Orchid Towers, 313 Valluvar Kottam High Road, Nungambakkam, Chennai 600 034, Tamil Nadu (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only):* **GNANAPRAKASAM, Andrew** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai 600 119, Tamil Nadu (IN). **VENUGOPAL, Sivasankaran** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai 600 119, Tamil Nadu (IN). **GANAPATHY, Veeramani** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai 600 119, Tamil Nadu (IN). **UDAYAMPALAYAM, Palanisamy, Senthilkumar** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai 600 119, Tamil Nadu (IN).

(74) Agents: **GOPALAN, Deepak, Sriniwas** et al.; K & S Partners, 84-C, C-6 Lane, Off Central Avenue, Sainik Farms, New Delhi 110 062 (IN).

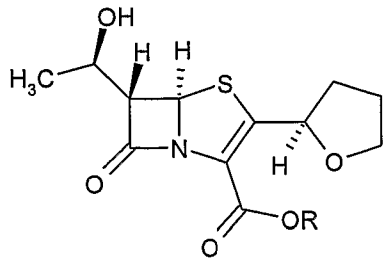
(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, **BR,** BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, **HR,** HU, **ID,** IL, IN, IS, **JP,**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

**Declaration under Rule** 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Ui))*

**Published:**
— *without international search report and to be republished upon receipt of that report*

(54) **Title:** PROCESS FOR THE PREPARATION OF BETA-LACTAM ANTIBIOTIC




(I)

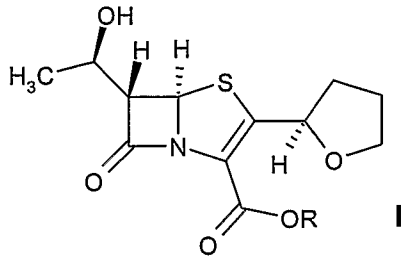
(57) **Abstract:** Novel process for the preparation of the Faropenem of formula (I) where, R is hydrogen, alkali metal salts such as sodium or potassium, or prodrug residue.

WO 2008/035153 A2

# PROCESS FOR THE PREPARATION OF β-LACTAM ANTIBIOTIC

## Field

An improved process relating to the preparation of β-lactam antibiotic of formula (I) or its hydrate in a pure form is described. The compound of formula (I) is known as Faropenem,




I

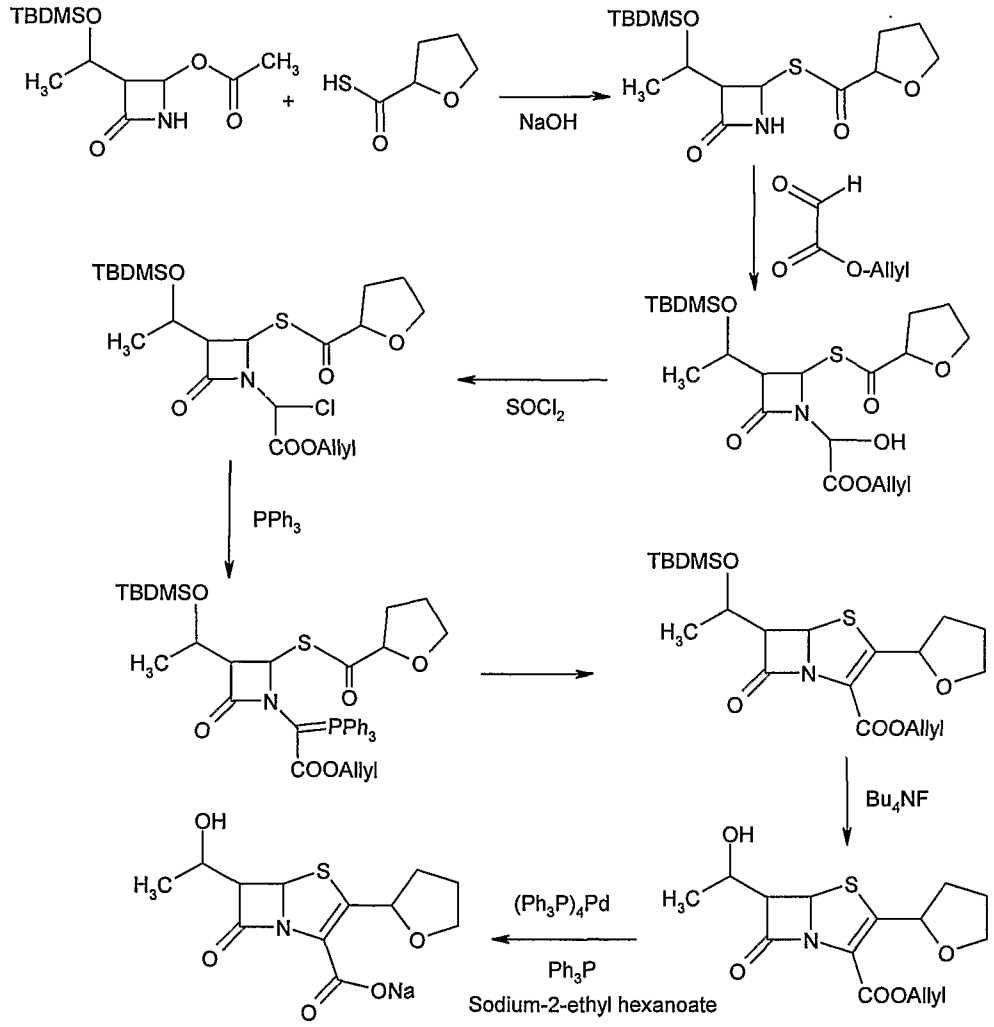
wherein, **R is** hydrogen, alkali metal salts such **as** sodium or potassium, or prodrug residue.

## Background

Faropenem is an orally active β-lactam antibiotic belonging to the penem group. Faropenem is chemically known as 6-(l-hydroxyethyl)-7-oxo-3-(oxolan-2-yl)-4-thia-l-azabicyclo[3.2.0]hept-2-ene-2-carboxylicacid. The known forms of Faropenem are Faropenem sodium and the prodrug form, Faropenem Medoxomil (also known as Faropenem Daloxate). In view of the importance of the compound of the formula (I), several synthetic procedures to prepare the compound have been reported.

US 4,997,829 provides process for the preparation of faropenem according to the following scheme. The process is exemplified with the allyl protected carboxyl group. One of the process involves the reaction of *A*-acetoxyazetidinone with tetrahydrothiofuroic acid, condensation with allyl glyoxalate in refluxing benzene, chlorination with thionyl chloride, reaction of triphenylphosphine with lutidine in hot THF, cyclization in refluxing toluene,

deprotection of silyl protecting group with tetrabutylammonium fluoride, treating with triphenylphosphine and, treating with sodium 2-ethylhexanoate and $(PPh_3)_4Pd$ to result faropenem sodium. The process exemplified utilizes benzene as solvent, which is not environmentally acceptable. Tetrabutylammonium fluoride was used as desilylating agent that is expensive. Even though the description teaches that optically active compounds can be employed, the examples utilized the dl-compound of tetrahydrothiofuroic acid further requiring resolution.




Methods are provided for the synthesis of series of penem compounds in *J Antibiotics* 1988, *41(11),* 1685-1693. The provided methods utilize

sulfonylazetidinone as the starting materials. As one of the procedures gives lesser yield, another procedure was adopted which uses silver salts.

Japanese patent, JP2949363 describes a process for deallylation and salt formation with an alkali metal salt of carboxylic acid in the presence of a catalytic amount of palladium complex for the preparation of faropenem. EP4 10727 describes a process for removing allyl group from a penem compound using cyclic 1,3-diketone such as dimedone.

The yield and quality of the final product is always less in the above prior art methods. With the continued research, the present inventors have undertaken extensive studies for developing a process for the preparation of compound of formula (I), which is commercially viable, involves simple techniques such as crystallizations, with improved yields and quality of the product, and with lesser reaction time. None of the prior art suggests or teaches the techniques provided herein.

## Objectives

The main objective herein is to provide a simple and commercially viable process for the preparation of compound of the formula (I) in pure form.

Another objective is to provide starting materials, intermediates and the final product in crystalline solids, which in turn provides improved purity and stability.

Another objective herein is to provide a simple and commercially viable process for the preparation of compound of the formula (I), which avoids chromatographic purification techniques.

## Summary

Process for the preparation of faropenem of formula (I), which comprises the steps of:

(a) reacting 4-acetoxyazetidinone (II) (AOSA) with alkali metal salt of tetrahydrothiofuroic acid of compound formula (III) in a solvent in presence or absence of base to produce the compound of formula (IV),

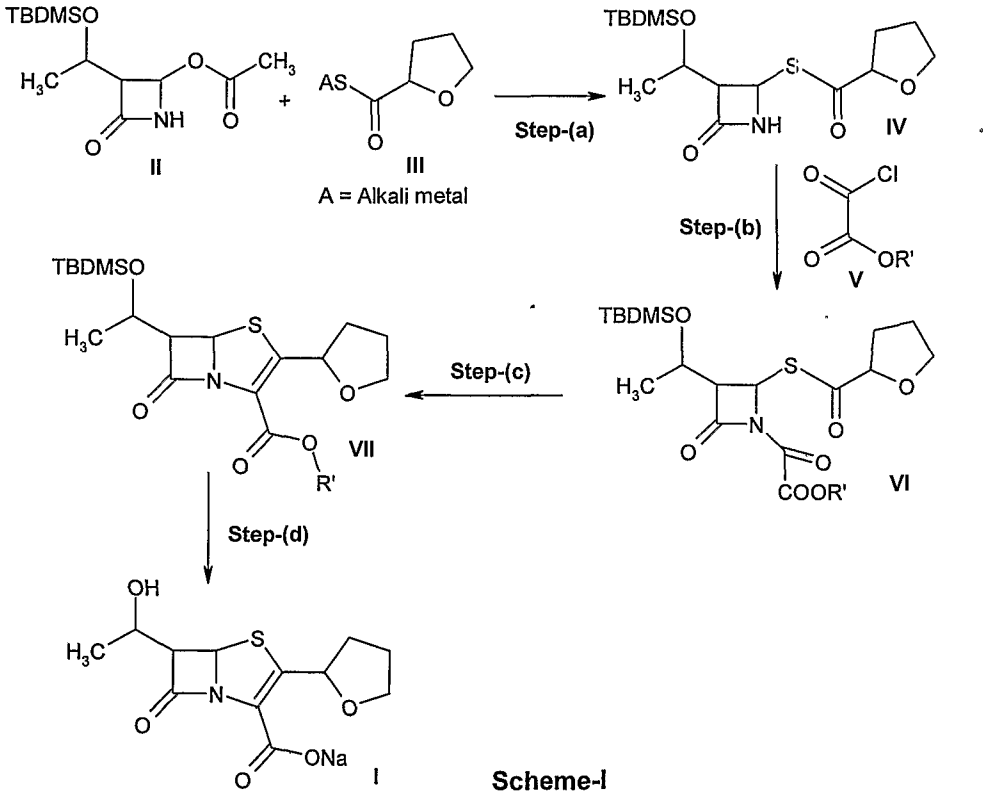
(b) condensing the compound of formula *(TV)* with oxalyl chloride of formula (V) wherein R' is p-nitrobenzyl (PNB), p-methoxybenzyl (PMB), p-nitrophenyl (PNP), p-methoxyphenyl (PMP), 3,4-dimethoxybenzyl, allyl, t-butyl, trityl, benzyl, benzhydryl (BH), or silyl and the like in presence or absence of base to produce compound of formula (VI).

(c) cyclizing the compound of formula (VI) wherein R' is as defined above in presence or absence of solvent and in presence trialkyl-, triaryl-, or trialkylaryl-phosphite to compound of formula (VII),

(d) deprotecting the compound of formula (VII), and

(e) isolating faropenem or its salts of compound of formula (I).

The process is shown in Scheme-I as given below:




Scheme-I

## Brief description of the drawings

Figure 1: PXRD pattern of sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid.

Figure 2: PXRD pattern of compound of formula (IV).

Figure 3: PXRD pattern of compound of formula (VI).

Figure 4: PXRD pattern of diprotected faropenem of compound of formula (VII).

Figure 5: PXRD pattern of compound of formula (VIII).

Figure 6: PXRD pattern of Faropenem sodium of compound of formula (I).

Figure 7: IR spectrum of sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid.

Figure 8: IR spectrum of compound of formula (IV).

Figure 9: IR spectrum of compound of formula (VI).

Figure 10: IR spectrum of diprotected faropenem of compound of formula (VII).

Figure 11: IR spectrum of compound of formula (VIII).

Figure 12: IR spectrum of Faropenem sodium of compound of formula (I).

## Description

In a first embodiment, alkali metal salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid of formula (III) preferably as a sodium salt was reacted with acetylazetidinone of compound of formula (II) in step (a) to form a compound of formula (IV), which is isolated as a crystalline solid. The reaction was also performed without isolating compound of formula (IV) as described in the example of one-pot process. It was surprisingly found that the use of sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid than the *in situ* generated one has more advantages in terms of better yield and complete conversion to product to obtain compound of formula (IV). The handling of solid sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid is easier and industrially advantageous than the liquid R(+)-tetrahydrofuran-2-thiocarboxylic acid and moreover the high purity of sodium salt avoids the formation of undesired products. The

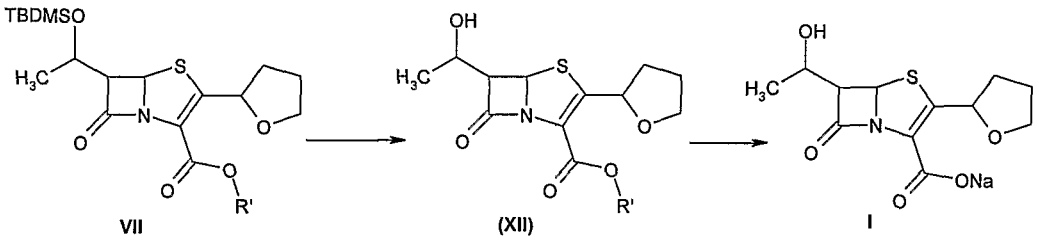
malodorous nature of the R(+)-tetrahydrofuran-2-thiocarboxylic acid is avoided by using its sodium salt. The compound of formula thus obtained following step (a) is crystalline in nature as evidenced from Powder X-Ray Diffraction (PXRD) and is shown in Figure 2.

The compound of formula (IV) is then converted to faropenem compound of formula (I) as given in scheme I, wherein the solvent used in step (a) is selected from acetone, dioxane, tetrahydrofuran (THF), water, diglyme, monoglyme, toluene and the like or the mixture thereof and the base used in step (a) is selected from inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate and the like. The base used in step (b) is selected from triethylamine, diisopropylethylamine, diisopropylamine, diethylamine, tetramethylguanidine (TMG), l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), l,5~diazabicyclo[4.3.0]non~5-ene (DBN), ammonia and the like or mixture thereof. Step (b) reaction was performed in a solvent that is chosen from dichloromethane (MDC), THF, diisopropyl ether, dioxane, toluene, sulfolane, monoglyme, diglyme, ethyl acetate, acetonitrile, water and the like or mixture thereof. The compound of formula (IV), either isolated as solid or prepared *in situ* is further reacted with oxalyl chloride of formula (V) preferably allyl oxalyl chloride to compound of formula (VI). The compound of formula (VI) was taken to the next step without the need to isolate compound (VI) as exemplified in one-pot process. Crystalline compound of formula (VI) was obtained following example 2 and its PXRD pattern is shown in Figure 3.

The solvent used in step (c) is selected from xylene, toluene, cycloalkanes, heptane, decane, decalin and the like or the mixture thereof preferably toluene and the trialkyl-, triaryl- or trialkylaryl-phosphite used is selected from triethyl phosphite, trimethyl phosphite, and the like. The Wittig ylide formation was carried out either in neat condition in triethyl phosphite or in the presence of solvent. The cyclization to form compound of formula (VII) can be carried out in two ways. First, Wittig ylide is formed using a neat condition

using triethyl phosphite and then adding suitable solvent followed by refluxing to cyclization. Second, triethyl phosphite and solvent were taken together followed by refluxing to obtain compound of formula (VII). When solvent is used for cyclization then lesser volume of solvent was added when compared to the prior art methods and the reaction was completed in substantially lesser reaction time. The improvement in the usage of lesser volume of solvent in step (c) leads to higher productivity in industrial process. The compound of formula (VII) obtained in step (c) was further taken to the next step without isolation as provided in one-pot process. The compound of formula (VII) obtained following example 3 resulted in a crystalline compound as is evidenced from PXRD as shown in Figure 4.

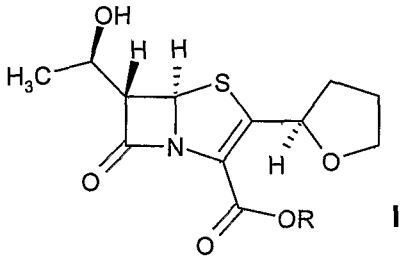
The deprotection that is given in step (d) could be performed stepwise such as desilylation of the hydroxy group to yield compound of formula (XII) followed by deprotecting at the carboxyl group or in one step using a suitable reagent resulting a compound of formula (I) as shown below. The desilylation is performed using ammonium hydrogen difluoride, tetrabutylammonium fluoride or the like in a suitable solvent selected from dimethylformamide, tetrahydrofuran, dioxane, acetone, ethyl acetate and water and the like or mixture thereof to yield compound of formula (XII). Upon completion of desilylation, the desilylated compound (XII) generated *in situ* was also taken to the next step as described in one-pot process. After desilylation, the desilylated compound (XII) thus obtained is crystalline in nature and its PXRD is shown in Figure 5.




The deprotection at the carboxyl group wherein protecting group is p-nitrobenzyl (PNB), benzhydryl (BH), p-methoxybenzyl (PMB), allyl or the like is carried out using conventional method such as using catalyst like palladium,

platinum, rhodium or its complexes using suitable solvents that does not affect the role of the reaction which include alcohols such as methanol and ethanol; haloallcyl solvents such as dichloromethane; esters such as ethyl acetate and methyl acetate; ethers such as tetrahydrofuran and dioxane; nitriles such as acetonitrile and propionitrile; ketones such as acetone and ethyl methyl ketone, aromatic hydrocarbon such as toluene, and water or mixture thereof. The carboxyl deprotection wherein protecting group is silyl, t-butyl is carried out using an acid like hydrochloric acid, formic acid in the above said solvent system. When the protecting group is allyl; tetrakistriphenylphosphine palladium(O) may also be used for deprotection. The process described herein provides novelty wherein the allyl moiety is easily removed by using palladium-carbon alone, whereas the prior art processes utilizes the costly and industrially not preferable tetrakistriphenylphosphine palladium(O). The use of $(PPh_3)_4Pd$ for deprotection is avoided which is replaced by Pd/C for the deprotection of allyl.

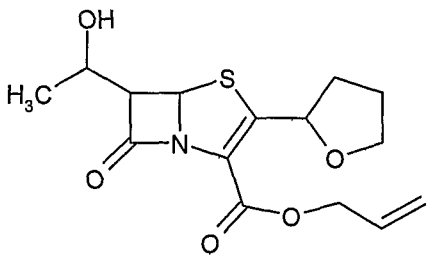
Process for the preparation of compound of formula (I)




I

wherein, R is hydrogen, alkali metal salt such as sodium or potassium, or prodrug residue, which comprises:

i) deprotection of the compound of formula (XII) using Pd/C in the presence of base, hydrogen or hydrogen source in a suitable solvent,




XII

and

ii) isolating faropenem or its salts of compound of formula (I),

wherein the improvement consists of using Pd/C for deprotection.

In deallylation process, base used is selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, sodium 2-ethylhexanoate or sodium lactate and the like and solvent used selected from water, ethyl acetate, methyl acetate, ethanol, methanol, tetrahydrofuran, acetonitrile, water and the like or mixture thereof.

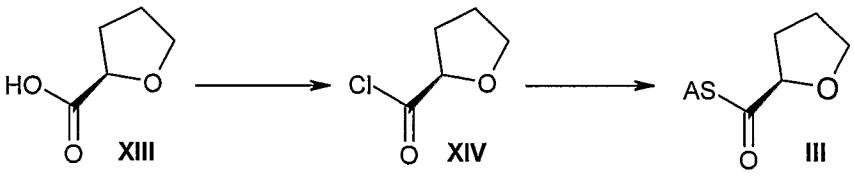
The final compound is directly isolated from the reaction mixture optionally by adding anti-solvent such as hexane, heptane, acetone, tetrahydrofuran, alcohols such as methanol, ethanol, isopropyl alcohol and the like, or by solvent evaporation to result compound of formula (I) in a crystalline or amorphous or as a mixture more conveniently as a alkali metal salt using appropriate salt source in a solvated or hydrated form or by adjusting pH. After deprotection, compound containing ethyl acetate organic layer was separated, wherein the deprotected compound was extracted into ethyl acetate layer and adding alkali metal source resulted in Faropenem. The present invention is suitable for the preparation of compound of formula (I) as a sodium salt preferably in a hydrate form, more preferably as Faropenem sodium hemipentahydrate. For further purification, when necessary, Faropenem sodium thus obtained is dissolved in water, optionally subjected to carbon treatment and acetone added then stirred under cooling to obtain highly pure (more than 99.9%) Faropenem sodium. The final compound, Faropenem sodium as obtained following example 5 is crystalline in nature, free-flowing, having good bulk-properties and suitable for subsequent formulation. Faropenem sodium thus obtained may also be micronized when required before formulation. The product obtained showed excellent stability, which render a desirable pharmaceutical form. Representative PXRD of Faropenem sodium is shown in Figure 6 and data in Table 1.

**Table 1:** PXRD data for Faropenem sodium

| 2-Theta | d(Å) | I% |
|---|---|---|
| 5.42 | 16.2968 | 100 |
| 9.92 | 8.9083 | 12.2 |
| 10.86 | 8.1404 | 89.6 |
| 12.56 | 7.0419 | 7.8 |
| 14.49 | 6.1051 | 19.9 |
| 16.06 | 5.5141 | 10.8 |
| 16.28 | 5.4399 | 15.4 |
| 16.66 | 5.3169 | 5.4 |
| 16.94 | 5.2293 | 5.9 |
| 18.04 | 4.9136 | 0.4 |
| 18.96 | 4.6773 | 66.1 |
| 19.42 | 4.5668 | 22.8 |
| 20.44 | 4.3412 | 5.3 |
| 21.10 | 4.2072 | 10.5 |
| 21.40 | 4.1487 | 7.6 |
| 21.70 | 4.0920 | 11.8 |
| 23.22 | 3.8275 | 12.3 |
| 23.62 | 3.7636 | 4.6 |
| 23.92 | 3.7179 | 1.0 |
| 24.96 | 3.5646 | 21.8 |
| 25.76 | 3.4559 | 0.4 |
| 26.48 | 3.3634 | 16.6 |
| 26.88 | 3.3141 | 10.1 |
| 27.22 | 3.2734 | 19.9 |
| 27.42 | 3.2502 | 17.9 |
| 28.72 | 3.1060 | 3.6 |
| 29.26 | 3.0496 | 4.4 |
| 29.54 | 3.0214 | 3.8 |
| 30.18 | 2.9588 | 1.6 |
| 31.44 | 2.8430 | 10.7 |
| 31.78 | 2.8134 | 16.1 |
| 32.58 | 2.7461 | 1.0 |
| 33.04 | 2.7088 | 1.3 |
| 33.56 | 2.6682 | 6.0 |
| 34.06 | 2.6302 | 4.0 |
| 34.40 | 2.6048 | 7.2 |
| 34.96 | 2.5643 | 0.5 |
| 35.50 | 2.5266 | 4.2 |
| 36.08 | 2.4875 | 2.1 |
| 36.60 | 2.4532 | 3.0 |
| 37.24 | 2.4125 | 1.6 |

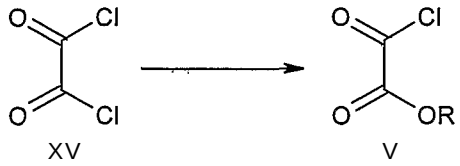
| | | |
|---|---|---|
| 37.94 | 2.3696 | 1.1 |
| 38.44 | 2.3399 | 15.5 |
| 38.76 | 2.3213 | 19.0 |
| 39.58 | 2.2751 | 2.1 |
| 40.22 | 2.2403 | 2.7 |
| 40.76 | 2.2118 | 6.8 |
| 41.92 | 2.1534 | 3.0 |
| 42.38 | 2.1309 | 2.3 |
| 42.89 | 2.1065 | 1.0 |
| 44.34 | 2.0413 | 9.7 |

One of the starting material, alkali metal salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid of compound of formula (III) may be prepared according to the Scheme-Ill. Chlorinating the compound of formula (XIII) using chlorinating agent such as phosphorous trichloride, phosphorous pentachloride, phosphorous oxychloride, thionyl chloride, oxalyl chloride and the like preferably using thionyl chloride in suitable solvent such as dichloromethane (MDC), toluene resulted acid chloride of the compound of formula (XIV). The acid chloride is then converted to sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid of compound of formula (III) as given in Example 6. The sodium salt of compound of formula (III) thus obtained is crystalline in nature and the PXRD is shown in Figure 1.




**Scheme-III**

AlIyI-, t-butyl- and p-nitrobenzyl oxalyl chloride are prepared from oxalyl chloride of formula (XV) using allyl-, t-butyl-, p-nitrobenzyl-alcohol, respectively, from ethereal solvents such as diethyl ether, diisopropyl ether (IPE) or tetrahydrofuran, dioxane or the like and preferably IPE, preferably in presence of Dimethylformamide (DMF). The preparation of allyl oxalyl chloride of formula (V) is exemplified in Example 7.



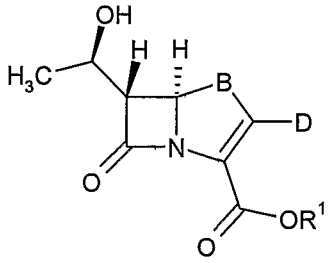

R = (a) Allyl or (b) PNB or (c) t-Butyl

Scheme-IV

Even though all of the intermediates and the final compounds are isolated as crystalline compounds in the present invention, it is obvious that the intermediates and the final products can also be isolated as amorphous materials depending on the rate and mode of addition. The reaction can also be performed in a single pot without isolating any of the intermediates as schematically given in Scheme-I to final Faropenem and exemplified in examples below.

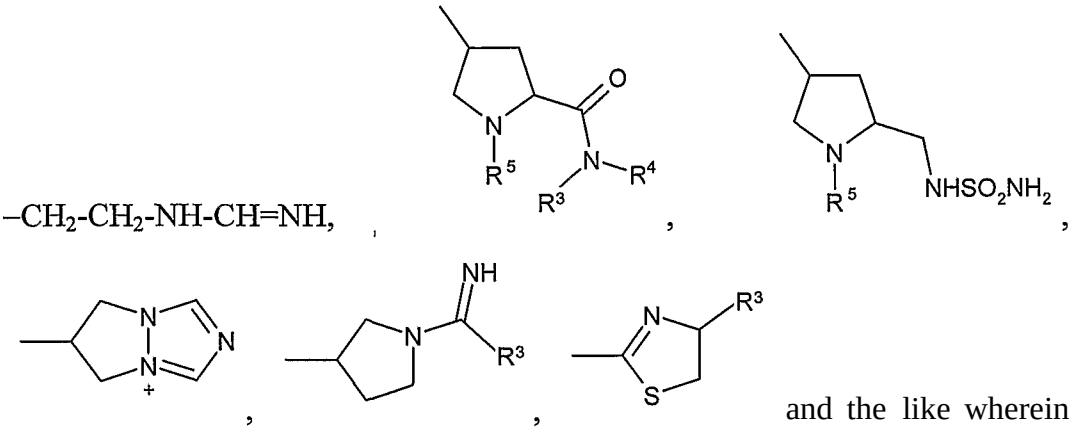
The foregoing technique has been found to be very attractive from commercial, technological and ecological perspective. The penems thus obtained can also be administered following conventional methods. The conventional pharmaceutical composition may also contain one or more of the following: chelating agent such as EDTA; or citric acid; or amino acids like arginine, lysine; or sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and the like.

Process described herein could also be followed for the preparation of compound of following formula,

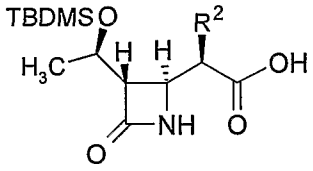



wherein B is a group of formula -S-, -O, -$CH_2$-, -$CH(R^Z)$-, -$CH_2$-$CH_2$-, -S-$CH_2$-, -0-$CH_2$-, in which $R^2$ is hydrogen or alkyl group, D is optionally substituted alkyl, aryl, heterocyclyl and the like, selected from tetrahydrofuran ring or substituted thiol of formula S-E, wherein E is optionally substituted alkyl,

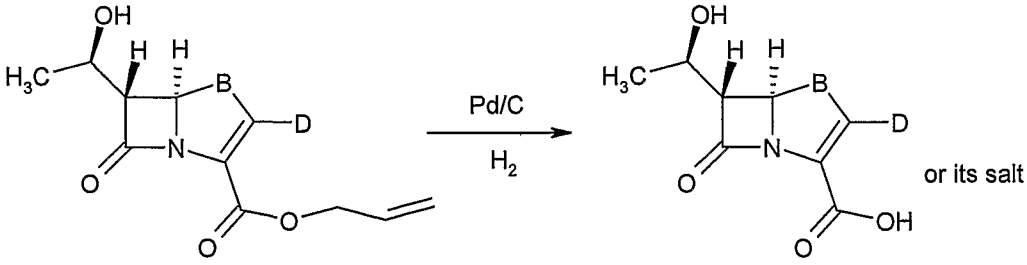
aryl, heterocyclyl and the like, which is selected from the group consisting of:



and the like wherein $R^3$ and $R^4$ independently represent hydrogen, $C_{1-10}$ alkyl, aryl or heteroaryl, or substituted $C_{1-10}$ alkyl, aryl, or heteroaryl, $R^5$ is hydrogen or protecting group and $R^1$ is hydrogen, alkali metal salts such as sodium or potassium, prodrugs or protecting group. Process as shown in Scheme-I is followed when B is -S- and when B denotes -CH($R^2$)-, then thiol side chain (S-E) is made to react with the compound of following formula, where $R^2$ is as described above.



Hence the deprotection of allyl group using Pd/C and hydrogen could be followed conveniently avoiding the use of palladium complex for such deprotection.



The following examples are provided by way of illustration only, which should not be construed to limit the scope of the invention.

**Process for the preparation of Faropenem**

**Example 1**

**Preparation of (1'R,2"R,3S,4R)-3-(l** '-tert-butyldimethylsiIyloxyethyl)-4-(2'-tetrahydrofuranoyIthio)-2-azetidinone **(IV)**

Sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid (67 g) in aqueous acetone was added slowly to a solution of 4-acetoxyazetidinone (AOSA) (100 g) in acetone (200 niL) and stirred for 3 h at 25 to 30 $^0$C in the pH range of 8.0 to 8.5 using sodium bicarbonate solution. After completion of the reaction, the product was extracted with ethyl acetate. The combined ethyl acetate layer was washed with saturated sodium bicarbonate solution and brine solution. Ethyl acetate was removed under vacuum completely and the title compound obtained was isolated using aqueous methanol, filtered and dried (120 g, 97 %).

**Example Ia**

**Preparation of (1'R,2"R,3S,4R)-3-(l** '-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone **(IV)**

Acetone (300 mL) was added to a solution of sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid (62 g) in water (300 mL). The pH was then adjusted to 9.0 to 9.5 using saturated sodium bicarbonate solution. A solution of 4-acetoxyazetidinone (AOSA) (100 g) in acetone (200 mL) was then added and stirred at room temperature in the pH of 8.0 to 8.5 using sodium bicarbonate solution. After completion of the reaction, the product was extracted with toluene. The combined toluene layer was washed with saturated sodium bicarbonate solution followed by water. Toluene layer was then concentrated by distillation under vacuum and taken for the next step as such.

**Example Ib**

**Preparation of** (l'R,2"R,3S,4R)-3-(l'-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone **(IV)**

To R(+)-tetrahydrofuran-2-thiocarboxylic acid (75 g), sodium hydroxide solution (IN $_5$ 600 mL) was added slowly. This solution was added slowly in to a

solution of AOSA (100 g) in acetone (300 mL) at 25 to 30 °C then stirred at 50 to 55 °C for 2 h maintaining pH 8.0 to 8.5 using IN sodium hydroxide solution. After completion of the reaction, the oily mass was separated and kept under high vacuum to remove traces of acetone. Weight of the oily product obtained was 130 g.

**Example 2**

**Preparation of** (3S,4R)-l-(aIlyIoxy)oxoacetyl-3-((R)-l-tert-butyldimethylsiIyloxyethyl)-4-(2-tetrahydrofuranyl)carbonyIthio-azetidin-2-**one (VI)**

(1'R,2''R,3S,4R)-3-(l '-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone (100 g) in dichloromethane (MDC) (600 mL) was cooled to 0 to 5 $^0$C under nitrogen atmosphere. Triethylamine (124 mL) was added to it followed by allyl oxalyl chloride (82 g) slowly at -10 to -5 $^0$C for 2 h. Cold water was added to the mass and the pH adjusted to 7.5 to 8.0 using saturated sodium bicarbonate solution then stirred. MDC layer was separated and it was washed with purified water. The MDC layer was concentrated under vacuum at 30 to 40 °C then the residue obtained was dissolved in methanol and added to purified water. The solid was filtered and dried (117 g, 90 %).

**Example 2a**

**Preparation of** (3S,4R)-l-(aIlyloxy)oxoacetyl-3-((R)-l-tert-butyldimethyIsilyloxyethyl)-4-(2-tetrahydrofuranyl)carbonyIthio-azetidin-2-**one (VI)**

(1'R,2''R,3S,4R)-3-(l '-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone was dissolved in toluene (1000 mL) and cooled to -10 to - 5 °C under nitrogen atmosphere. Triethylamine (124 mL) was added slowly followed by allyl oxalyl chloride (82 g) at -5 to -10 °C. After completion of the reaction, cold water (300 mL) was added to the mass, washed with dilute hydrochloric acid followed by saturated sodium bicarbonate solution. Toluene layer was separated and washed with purified water. The toluene layer

was concentrated under vacuum then the residue dissolved in methanol (300 mL) and added to purified water (200 mL) at 10 -15 °C. The solid obtained was filtered and dried. Dry weight of the product: 145 - 155 g.

**Example 2b**

**Preparation of** (3S,4R)-l-(allyIoxy)oxoacetyl-3-((R)-l-tert-butyIdimethyIsilyloxyethyl)-4-(2-tetrahydrofuranyl)carbonylthio-azetidin-2-**one (VI)**

(1'R,2''R,3S,4R)-3-(l '-tert-butyldimethylsilyloxyethyl)-4-(2'-tetany drofuranoylthio)-2-azetidinone (120 g) in toluene (1000 mL) was cooled to -10 to -15 °C under nitrogen. Triethylamine (107 mL) was added to it followed by allyl oxalyl chloride (80 g) slowly at -10 to -15 °C and stirred. Purified water was added to the mass and the pH adjusted to 2.0 to 3.0 using HCl solution (1:1). Toluene layer was separated, washed with sodium bicarbonate solution, purified water and charcoalised. The toluene layer was distilled-off completely under vacuum at 50 to 60 °C then the residue obtained dissolved in methanol and water added. The mass was stirred under cooling. The solid obtained was filtered and dried under vacuum (140-150 g).

**Example 3**

**Preparation of** allyl (l'R,2''R,5R,6S)-6-(l'-tert-butyldimethylsilyloxyethyl)-2-(2''-tetrahydrofuranyl)penem-3-carboxylate **(VII)**

Compound of formula (VI) (100 g) was dissolved in triethyl phosphite (74 g) and stirred for 4 h at 60 °C under nitrogen atmosphere. Toluene (1500 mL) was then added. The mixture was then heated to 105 to 110 $^0$C and stirred under nitrogen for 15 h. Toluene was distilled under vacuum completely. Methanol was added to the mass and cooled to 0 $^0$C. The solid mass obtained was stirred, filtered and dried (79 g, 80 %).

**Example 3a**

**Preparation of allyl** (l'R,2''R,5R,6S)-6-(l'-tert-butyldimethylsilyloxyethyl)-2-(2''-tetrahydrofuranyl)penem-3-carboxylate **(VII)**

Compound of formula (VI) (100 g) was dissolved in triethyl phosphite (74 g) and stirred at 55 to 65 $^0$C under nitrogen atmosphere. Toluene (1500 niL) was then added. The mixture was then heated to 105-110 °C and stirred under nitrogen for 15 to 35 h. Toluene was distilled under vacuum. Isopropyl alcohol was added to the mass and cooled to 0 °C. The solid mass obtained was filtered, washed with isopropyl alcohol and dried under vacuum (79 g, 80 %).

**Example 4**

**Preparation of** allyl (l'R,2"R,5R,6S)-6-(l'-hydroxyethyI)-2-(2"-tetrahydrofuranyl)penem-3-carboxylate **(XII)**

Compound (VII) (100 g), ammonium hydrogen difluoride (52 g), N-methylpyrrolidinone (NMP) (150 mL) and DMF (500 mL) were taken and stirred at room temperature for 24 to 32 h. The reaction mass was quenched into the mixture of water-ethyl acetate and stirred at room temperature. The ethyl acetate layer was separated and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate layer was washed with purified water followed by saturated sodium bicarbonate solution and brine solution. The ethyl acetate layer was charcoal treated. Ethyl acetate was distilled off and to the residue, IPE or water added. The title compound obtained was filtered, washed with IPE and dried (75 g, 95 %).

**Example 4a**

**Preparation of** allyl **(1'R,2"R,5R,6S)-6-(l'**-hydroxy ethyl)-2-(2"-tetrahydrofuranyl)penem-3-carboxylate **(XII)**

Compound (VII) (100 g), ammonium hydrogen difluoride (55 g), N-methylpyrrolidinone (NMP) (150 mL) and Dimethylformamide (DMF) (500 mL) were taken and stirred at room temperature for 24 to 32 h. The reaction mass was quenched into the mixture of water-ethyl acetate and stirred at room temperature. The ethyl acetate layer was separated and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate layer was washed with purified water followed by saturated sodium bicarbonate solution. The ethyl

acetate layer was charcoal treated. Ethyl acetate layer was partially distilled and taken for the next step.

**Example 4b**

**Preparation of compound of formula (XII)**

Compound of formula (VII) (10 g) was dissolved in THF and cooled to 0 $^0$C. Acetic acid was added slowly to the mass and IM solution of tetra-n-butyl ammonium bromide or tetra-n-butyl ammonium fluoride in THF (70 mL) added at 0 to 5 °C. The temperature of the reaction mass was stirred at room temperature for 24 h. THF was distilled out from the mass and the residue quenched into cold water (100 mL) at 0 to 5 °C. The product was extracted with ethyl acetate from the aqueous layer. The combined ethyl acetate layer was washed with purified water followed by saturated sodium bicarbonate solution and brine solution. Ethyl acetate was distilled and the mass obtained taken for next step as such.

**Example 5**

**Preparation of Faropenem sodium (I)**

Compound of formula (XII) (70 g), Pd/C, sodium bicarbonate, purified water (350 mL) and ethyl acetate (560 mL) were taken in an autoclave and maintained 5 to 10 kg pressure of hydrogen gas for 2-5 h. After completion of the reaction, the Pd/C was filtered and ethyl acetate layer separated. The pH of the aqueous mass was adjusted to 1.5 and extracted with ethyl acetate. The combined ethyl acetate layer was carbon treated. Sodium 2-ethylhexanoate in ethyl acetate was added slowly and stirred for 1 h. The precipitated title compound was filtered under vacuum, washed with acetone and dried (60 g, 80 %).

**Example 5a**

**Preparation of Faropenem sodium (I)**

Sodium bicarbonate and Pd/C in purified water were added to ethyl acetate layer containing compound of formula (XII) in an autoclave and

maintained 5 to 10 kg pressure of hydrogen gas. After completion of the reaction, the Pd/C was filtered and ethyl acetate layer separated. The pH of the aqueous mass was adjusted to 1.5 and extracted with ethyl acetate. The combined ethyl acetate layer was carbon treated. Sodium-2-ethylhexanoate in ethyl acetate was added slowly and stirred. The precipitated title compound was filtered, washed with ethyl acetate followed by acetone and dried. The solid obtained was dissolved in purified water and acetone was added slowly. The slurry mass was cooled to 0 to 5 $^0$C and stirred. The solid obtained was filtered, washed with acetone and dried under vacuum.

**Example 6**

**Preparation of sodium salt of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid**

**Step (A)**

**Preparation of** R(+)-tetrahydrofuran-2-carbonyl **chloride**

R(+)-Tetrahydrofuran-2-carboxylic acid (100 g) was dissolved in MDC (200 niL) and thionyl chloride (80 mL) added slowly over 2 h. The reaction mass was stirred for 2 h at room temperature. Excess thionyl chloride and MDC was removed under vacuum. Product was distilled under high vacuum at 45 to 55 °C. Weight of the title compound obtained was 95 g.

**Step (B)**

**Preparation of sodium salt of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid**

R(+)-Tetrahydrofuran-2-carbonyl chloride (95 g) was added to a solution of sodium sulfide (85 g) in purified water (360 mL) and MDC (450 mL) at -10 to -15 °C over 30 min. and stirred at -10 to -15 $^0$C for 1 h. After completion of the reaction, MDC layer was separated out and product extracted using ethyl acetate by adjusting pH 1.5. The combined ethyl acetate layer was washed with brine solution then stirred with carbon and sodium sulphate, filtered and washed with ethyl acetate. Sodium 2-ethylhexanoate in ethyl acetate was added slowly for 1 h. The solid was filtered, washed with ethyl acetate and dried under vacuum. Weight of the title compound obtained was 85 g (Moisture content: 8-12 %).

**Example 6a**

**Preparation of sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid**

**Step (A)**

**Preparation of acid chloride of** R(+)-tetrahydrofuran-2-carboxylic **acid**

R(+)-Tetrahydrofuran-2-carboxylic acid (100 g) was dissolved in dichloromethane (MDC) (300 mL) and thionyl chloride (80 mL) added slowly. The reaction mass was stirred for 2 h at 30 -35 $^0$C. Excess thionyl chloride and MDC were removed under vacuum at 40 $^0$C. This was taken for next step as such.

**Step (B)**

**Preparation of sodium salt of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid**

A solution of sodium sulfide (125 g) in purified water (220 mL) was added slowly into the solution of acid chloride of R(+)-tetrahydrofuran carboxylic acid in MDC at -10 to -15 °C and stirred. After completion of the reaction, MDC layer was separated and product extracted using ethyl acetate after adjusting to acidic pH. The combined ethyl acetate layer was then washed with brine solution, dried with sodium sulphate, filtered and washed with ethyl acetate. Sodium 2-ethylhexanoate (156 g) in ethyl acetate (200 mL) was added slowly at 10 to 15°C and stirred. The solid obtained was filtered, washed with ethyl acetate and dried under vacuum. Weight of the product obtained was 100 g with the moisture content: 8 - 12 %.

**Example 6b**

**Preparation of sodium salt of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid**

**Step (A)**

**Preparation of acid chloride of** R(+)-tetrahydrofuran-2-carboxylic **acid**

R(+)-Tetrahydrofuran-2 -carboxylic acid (100 g) was dissolved in dichloromethane (MDC) (300 mL) and thionyl chloride (80 mL) added slowly over 5 min. The reaction mass was stirred for 2 h at 30 -35 $^0$C. Excess thionyl chloride and MDC was removed under vacuum at 40 °C. The crude mass

obtained was dissolved in MDC under nitrogen atmosphere and continued to next step as such.

**Step (B)**

**Preparation of sodium salt of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid**

A solution of sodium sulfide (108 g) in purified water (220 mL) was added slowly into the MDC solution containing acid chloride of R-(+)-tetrahydrofuran carboxylic acid at -8 to -12 °C and stirred at -5 to -10 °C. After completion of the reaction, purified water was added. The MDC layer was separated and product extracted using ethyl acetate after adjusting the pH to 1.8-2.0. The combined ethyl acetate layer was concentrated by distillation. Sodium-2-ethylhexanoate (165 g) in ethyl acetate (800 mL) was added and stirred at 2 to 5 °C for 1 h. The solid obtained was filtered, washed with ethyl acetate and dried under vacuum. Weight of the product was 90-100.g.

**Example 6c**

**Preparation of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid (III)**

**Step (A)**

**Preparation of acid chloride of** R(+)-tetrahydrofuran-2-carboxylic **acid**

R(+)-Tetrahydrofuran-2-carboxylic acid (100 g) was dissolved in toluene (100 mL) and thionyl chloride (80 mL) was added slowly. The reaction mass was heated to 65-70 °C and stirred for 2 h. Excess thionyl chloride and toluene were removed under vacuum. Product was distilled under high vacuum at 50 to 55 °C. Weight of the product was 70 to 80 g.

**Step (B)**

**Preparation of** R(+)-tetrahydrofuran-2-thiocarboxylic **acid (III)**

Potassium hydroxide (90 g) was taken in water-ethanol mixture then cooled to - 5 to 0 $^0$C. $H_2S$ gas [prepared by slow addition of con. HCl (500 mL) to a solution of sodium sulfide (250 g) in water (500 mL)] was passed through the mass to saturate the solution. Acid chloride of R(+)-tetrahydrofurancarboxylic acid (75 g) was added slowly at 0 °C and stirred for 2 h at 25 to 30 °C. After completion of the reaction, ethanol was distilled under

vacuum and the mass dissolved in cold water (200 mL). The pH was adjusted to 1.2 to 1.5 using 1:1 HCl (150 mL). The product was extracted by using ethyl acetate (500 mL) and the ethyl acetate removed under vacuum. Weight of the product (oily mass): 65 to 70 g.

**Example 7**

**Preparation of** allyl **oxalyl chloride**

AUyI alcohol (23 g) in diisopropyl ether (IPE) (100 mL) was added slowly to oxalyl chloride (50 g) in IPE (200 mL) at 0 to - 5 °C over 2 h. and stirred at 0 °C for 25 h. The solvent was removed under vacuum. The allyl oxalyl chloride was distilled under high vacuum at 50 to 70 °C (32 g).

**Example 7a**

**Preparation of** allyl **oxalyl chloride**

Oxalyl chloride (208 g) followed by DMF (1 mL) was added to cold diisopropyl ether (500 mL). Allyl alcohol (100 g) was then added at -5 to 0 °C. The reaction mass was stirred for 2 h at - 2 to 0 $^0$C and the solvent distilled off at 40-45 °C under vacuum. The product, allyl oxalyl chloride was distilled under vacuum at 80 to 90 °C (150 g).

**Example 7b**

**Preparation of allyl** oxalyl **chloride**

Oxalyl chloride (208 g) followed by DMF (1 mL) was added to cold diisopropyl ether (500 mL). Allyl alcohol (100 g) was then added at 0 to -5 $^0$C. The reaction mass was stirred for 2-3 h at 0 to 2 °C and the solvent distilled off at 35-40 °C under vacuum. The product, allyl oxalyl chloride was distilled under vacuum and stored under nitrogen (150-170 g).

**Example 8**

**One-pot process for the preparation of Faropenem sodium:**

Sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid (67 g) in aqueous acetone was added slowly to a solution of AOSA (100 g) in acetone (200 mL) and stirred for 3 h at pH 8.0 to 8.5 using sodium bicarbonate solution. After completion of the reaction, the product was extracted with toluene. The combined toluene layer was washed with saturated sodium bicarbonate solution and brine solution. Toluene was removed under vacuum completely and the mass obtained, 3-(l'-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone was directly taken for next step.

3-(r-tert-Butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone obtained was dissolved in toluene (1000 mL) and cooled to -10 to -5 °C under nitrogen. Triethylamine (124 mL) was added to it followed by allyl oxalyl chloride (82 g) at -10 to- 5 $^0$C for 2 h. After completion of the reaction, cold water was added to the mass and washed with dilute hydrochloric acid and sodium bicarbonate solution. Toluene layer was separated and washed with purified water. The toluene layer containing compound of formula (VI) was concentrated under vacuum at 50 to 60 °C and taken for next step as such.

Compound of formula (VI) (150 g) was dissolved in triethyl phosphite (150 mL), heated to 60 $^0$C and stirred under nitrogen atmosphere. Toluene (3000 mL) was added, heated to 100 to 110 °C and stirred for 20- 24 h. Toluene was distilled under vacuum completely. Product obtained, allyl (1'R,2''R,5R,6S)-6-(l 5-tert-butyldimethylsilyloxyethyl)-2-(2''-tetrahydrofuranyl) penem-3-carboxylate (VII) was directly taken for next step.

Compound (VII) obtained was dissolved in DMF (700 mL) at 30 °C. Ammonium hydrogen difluoride (80 g) and NMP (210 mL) were added and stirred at room temperature for 25 to 35 h. The reaction mass was quenched into a mixture of water-ethyl acetate and stirred at room temperature. The ethyl acetate layer was separated and the aqueous layer extracted with ethyl acetate.

The combined ethyl acetate layer was washed with water followed by saturated sodium bicarbonate solution. The ethyl acetate layer was charcoal treated. The ethyl acetate layer containing allyl (l'R,2"R,5R,6S)-6-(l'-hydroxyethyl)-2-(2"-tetrahydrofuranyl)penem-3-carboxylate (XII) was partially distilled and taken for the next step.

The ethyl acetate layer containing compound of formula (XII), Pd/C, sodium bicarbonate and purified water (1000 mL) were taken in an autoclave and maintained 5 to 10 kg pressure of hydrogen gas for 2-5 h. After completion of the reaction the Pd/C was filtered off and ethyl acetate layer separated. The pH of the mass was adjusted to 1.5 and extracted with ethyl acetate. The aqueous layer was extracted again with ethyl acetate twice. The combined ethyl acetate layer was carbon treated. Sodium-2-ethylhexanoate in ethyl acetate was added slowly and stirred. The precipitated title compound was filtered under vacuum, washed with acetone and dried. Dry weight of the product: 65-75 g.

**Example 9**

**Purification of Faropenem sodium**

Crude Faropenem sodium (50 g) was dissolved in purified water (200 mL) at 25-30 $^0$C. The solution was charcoalised. Acetone (1500 mL) was added. The reaction mass was stirred further for 10 min. The precipitated solid was cooled to 0 –2 °C then filtered, washed with acetone and dried at room temperature. Weight of pure Faropenem sodium is 43 to 46 g (Purity 99.95%).

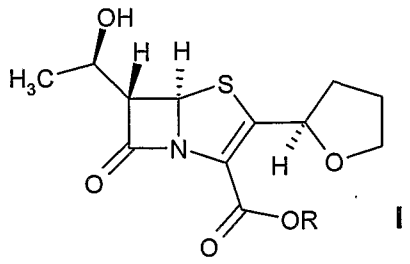
**Example 9a**

**Purification of Faropenem sodium**

Crude Faropenem sodium (50 g) was dissolved in purified water (200 mL) at 25-30 °C. Acetone (150O mL) was added. The reaction mass was stirred further for 10 min. The precipitated solid was cooled to 0-2 °C then filtered, washed with acetone and dried at room temperature. Weight of pure Faropenem sodium is 43 to 46 g (Purity 99.95%).

**We claim:**

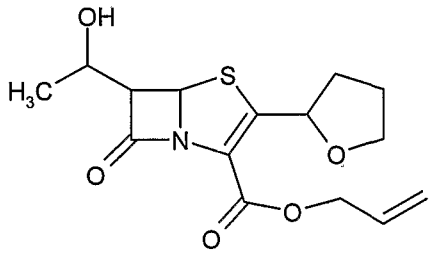
1. Process for the preparation of compound of formula (I)




I

wherein, R is hydrogen, alkali metal salt such as sodium or potassium, or prodrug residue, which comprises:

i) deprotection of the compound of formula (XII) using Pd/C in the presence of base, hydrogen source in a suitable solvent,




XII

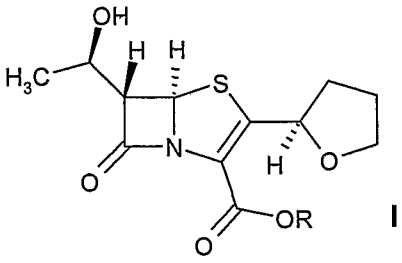
and

ii) isolating faropenem or its salts of compound of formula (I),

wherein the improvement consists of using Pd/C for deprotection.

2. The process according to claim 1 wherein base used is selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, sodium 2-ethylhexanoate or sodium lactate and solvent used selected from water, ethyl acetate, methyl acetate, ethanol, methanol, tetrahydrofuran, acetonitrile, water or mixture thereof.

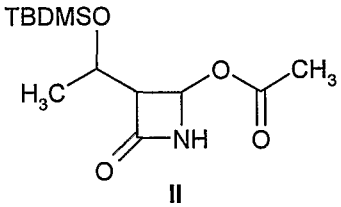
3. Process for the preparation of compound of formula (I)




I

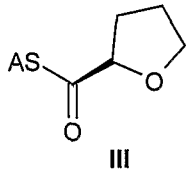
wherein, R is hydrogen, alkali metal salt such as sodium or potassium, or prodrug, which comprises the steps of:

(a) reacting 4-acetoxyazetidinone (II),



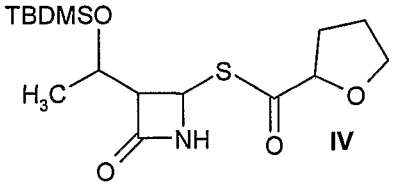

II

with alkali metal salt of tetrahydrothiofuroic acid of compound of formula (HI),




III

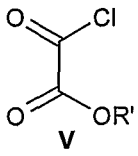
to produce the compound of formula (IV),




IV

;

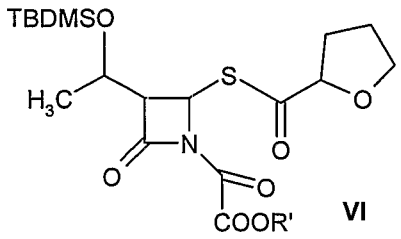
(b) condensing the compound of formula (IV) with oxalyl chloride of formula (V),




V

wherein R' is carboxyl protecting group in presence or absence of base to produce compound of formula (VI);

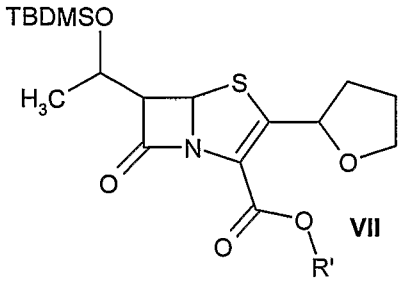
(c) cyclizing the compound of formula (VI),




VI

wherein R' is carboxyl protecting group optionally in presence of solvent and in presence of trialkyl-, triaryl-, or trialkylaryl-phosphite to compound of formula (VII);

(d) deprotecting the compound of formula (VII),




VII

and

(e) isolating faropenem or its salts of compound of formula (I),

wherein the improvement consists of one or more of the following:

(i) use of alkali metal salt of tetrahydrothiofuroic acid in step (a),

(ii) deprotection of allyl group by Pd/C in step (d)

(iii) extracting the final compound in ethyl acetate, and

(iv) conducting steps (a) to (d) in a single pot.

4. Process according to claim 3 wherein the carboxyl protecting group R' is optionally substituted alkyl, optionally substituted aryl, or optionally substituted alkenyl group, which is selected from p-nitrobenzyl (PNB), p-methoxybenzyl (PMB), p-nitrophenyl (PNP), p-methoxyphenyl (PMP), 3,4-dimethoxybenzyl, allyl, t-butyl, trityl, benzyl, benzhydryl (BH), or silyl group.

5. Process according to claim 3 wherein solvent used in step (a) is selected from acetone, dioxane, tetrahydrofuran, water, diglyme, monoglyme, toluene and mixture thereof.

6. Process according to claim 3 wherein base used in step (b) is selected from triethylamine, diisopropylethylamine, diisopropylamine, diethylamine, tetramethylguanidine (TMG), l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), l,5-diazabicyclo[4.3.0]non-5-ene (DBN) ammonia and mixture thereof.

7. Process according to claim 3 wherein solvent used in step (b) is selected from dichloromethane, tetrahydrofuran, diisopropyl ether, dioxane, toluene, sulfolane, monoglyme, diglyme, ethyl acetate, acetonitrile and mixture thereof.

8. Process according to claim 3 wherein solvent used in step (c) is selected from xylene, toluene, cycloalkanes, heptane, decane, decalin and mixture thereof.

9. Process according to claim 3 wherein solvent used in step (d) for desilylation is selected from dimethylformamide, tetrahydrofuran, dioxane, acetone and mixture thereof and solvent used for the deprotection at the carboxyl group is selected from methanol, ethanol, dichloromethane, ethyl acetate, methyl acetate, tetrahydrofuran, dioxane, acetonitrile, propionitrile, acetone, ethyl methyl ketone, toluene and water or mixture thereof.

10. Crystalline ,sodium salt of R(+)-tetrahydrofuran-2-thiocarboxylic acid as shown in Figure 1.

11. Crystalline (1'R,2''R,3S,4R)-3-(l '-tert-butyldimethylsilyloxyethyl)-4-(2'-tetrahydrofuranoylthio)-2-azetidinone (IV) as shown in Figure 2.

12. Crystalline (3S,4R)-l-(allyloxy)oxoacetyl-3-((R)-l-tert-butyldimethylsilyloxyethyl)-4-(2-tetrahydrofuranyl)carbonylthio-azetidin-2-one (VI) as shown in Figure 3.

13. Crystalline allyl (1'R,2"R,5R,6S)-6-( 1'-tert-butyldimethylsilyloxyethyl)-2-(2"-tetrahydrofuranyl)penem-3-carboxylate (VII) as shown in Figure 4.

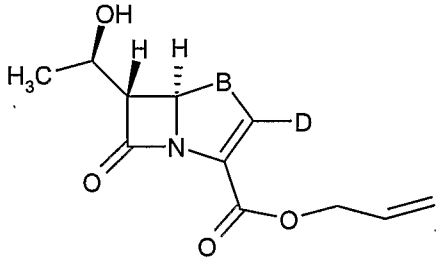
14. Crystalline allyl (l'R,2"R,5R,6S)-6-(l'-hydroxyethyl)-2-(2"-tetrahydrofuranyl)penem-3-carboxylate (XII) as shown in Figure 5.

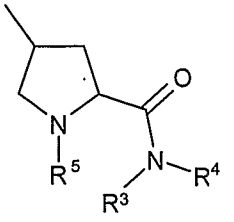
15. Crystalline Faropenem sodium of compound of formula (I) as shown in Figure 6.

16. Crystalline Faropenem sodium with a characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 5.4+0.1°, 10.9±0.1°, 19.0+0.1°, 19.4+0.1° and 25.0+0.1°.

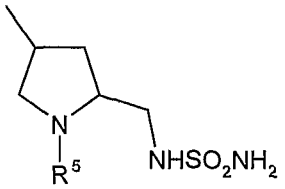
17. Production of Faropenem daloxate from compound of formula (I) according to the process of any preceding claims.

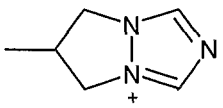
18. Deprotection of compound of following formula using Pd/C,

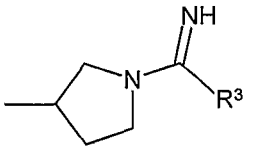


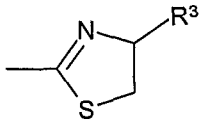

to its corresponding acid or salts thereof, wherein B is a group of formula -S-, -O-, -$CH_2$-, -CH($R^2$)-, -$CH_2$-$CH_2$-, -S-$CH_2$-, -0-$CH_2$-, in which $R^2$ is hydrogen or alkyl group, D is optionally substituted alkyl, aryl or heterocyclyl, selected from tetrahydrofuran ring or substituted thiol of formula S-E, wherein E is optionally substituted alkyl, aryl or heterocyclyl, which is selected from the group consisting of: -$CH_2$-$CH_2$-NH-CH=NH, 

,



,


,


,


and the like wherein $R^3$ and $R^4$ independently represent hydrogen, $C_{1-10}$ alkyl, aryl or heteroaryl, or substituted $C_{1-10}$ alkyl, aryl, or heteroaryl, and $R^5$ is hydrogen or protecting group.

5

FIGURE-1

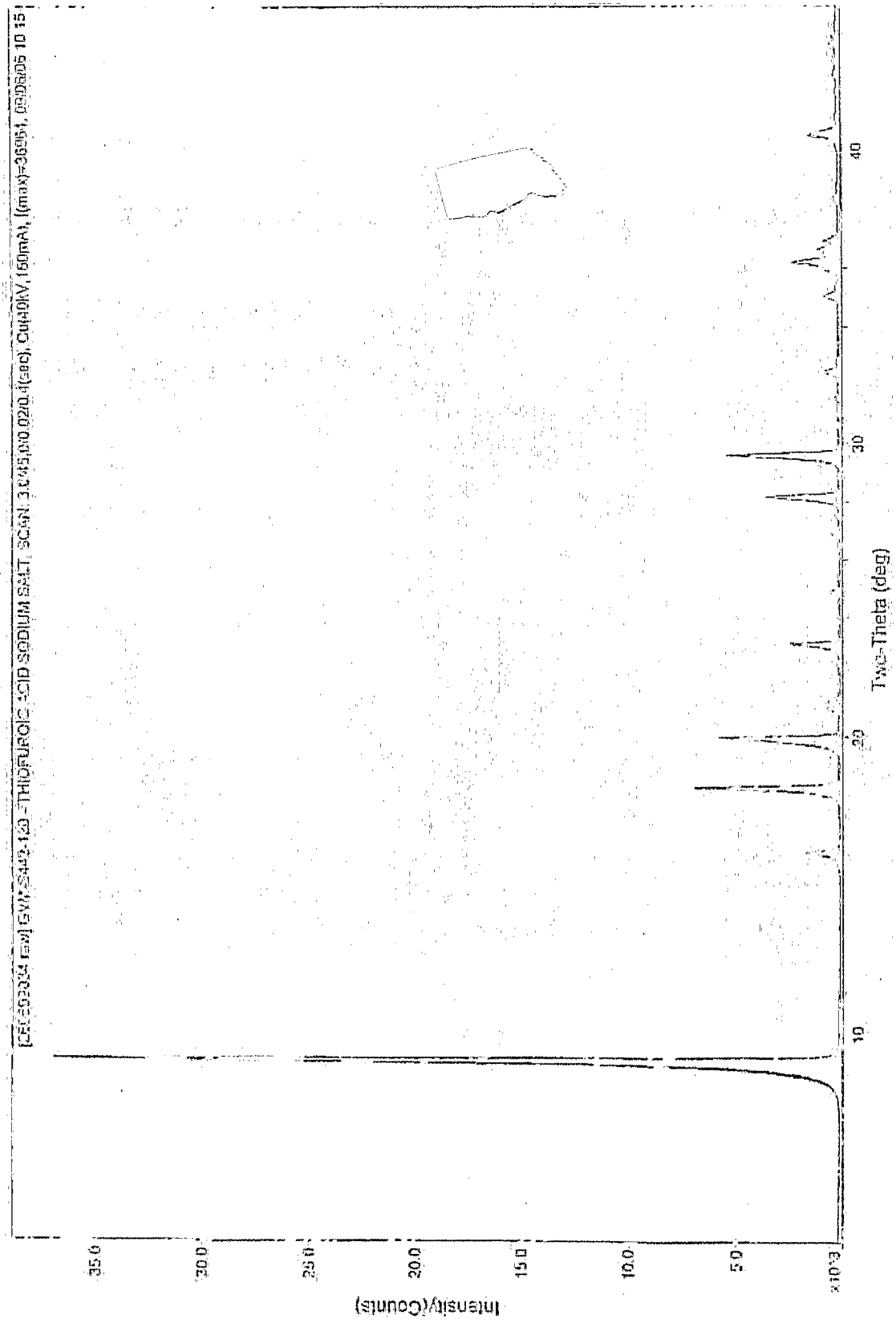

Intensity(Counts)
x10^3
35.0
30.0
25.0
20.0
15.0
10.0
5.0
10
20
30
40
Two-Theta (deg)

FIGURE-2

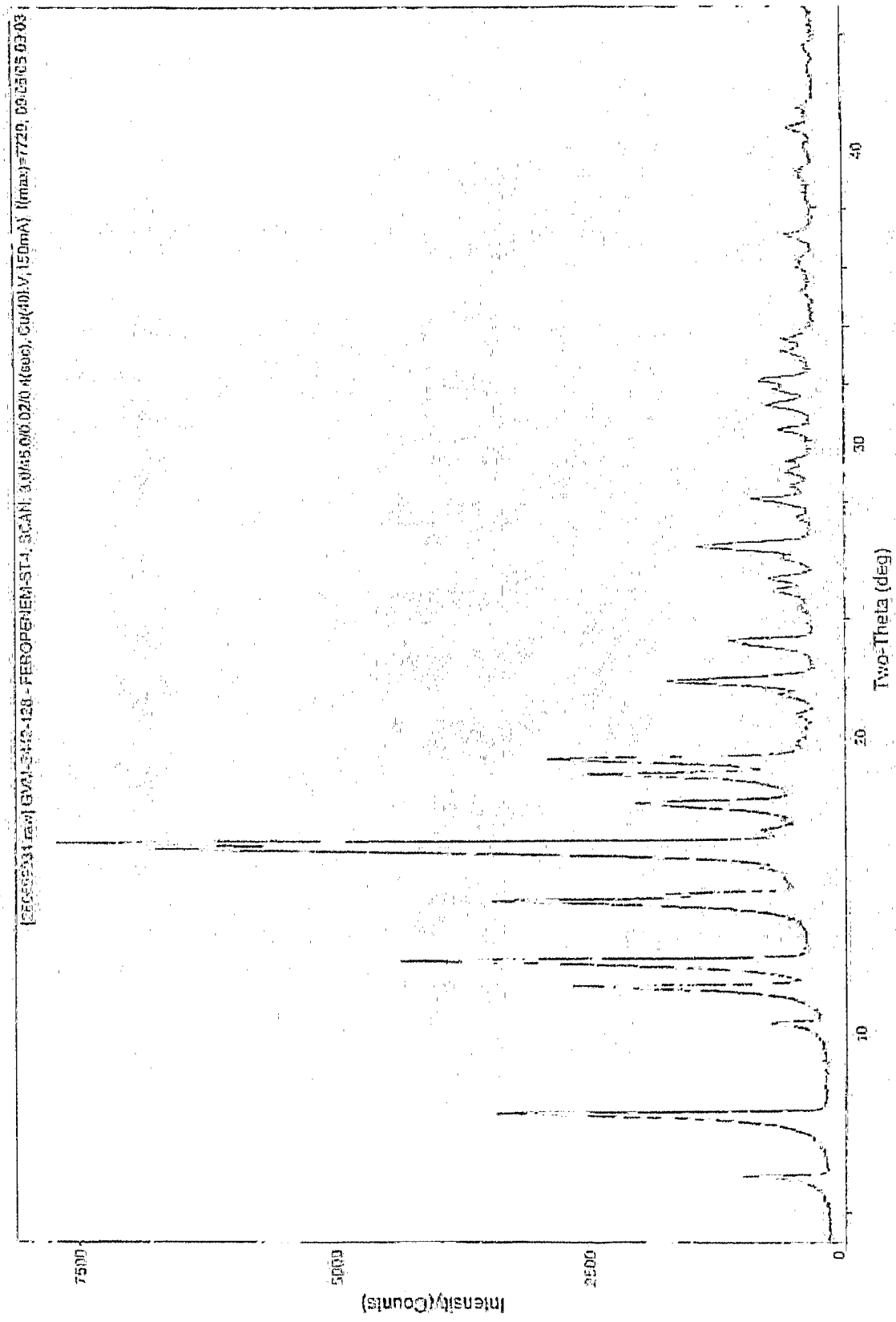


FIGURE-3

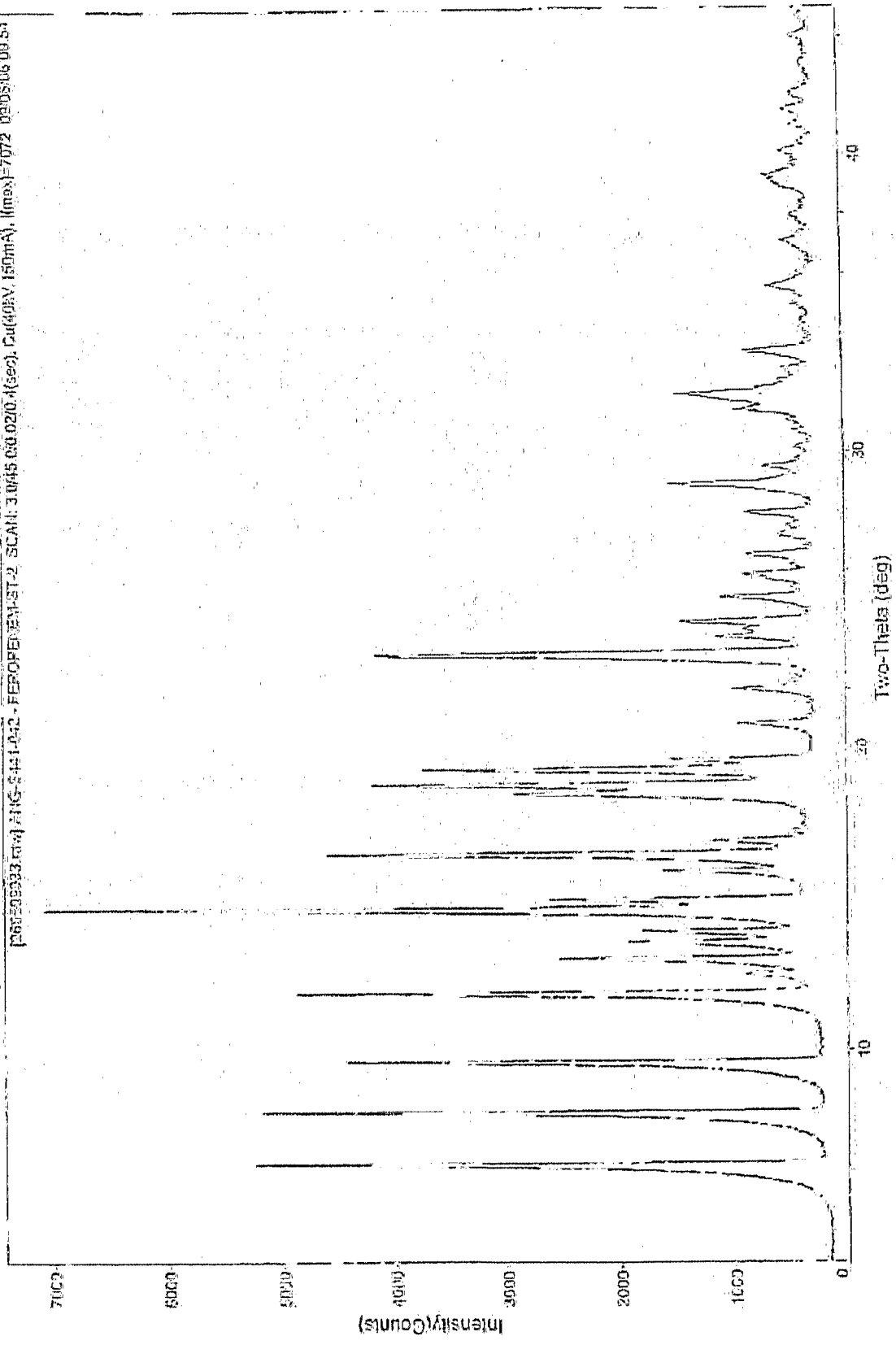

Intensity(Counts)
Two-Theta (deg)
0
10
20
30
40
1000
2000
3000
4000
5000
6000
7000

FIGURE-4

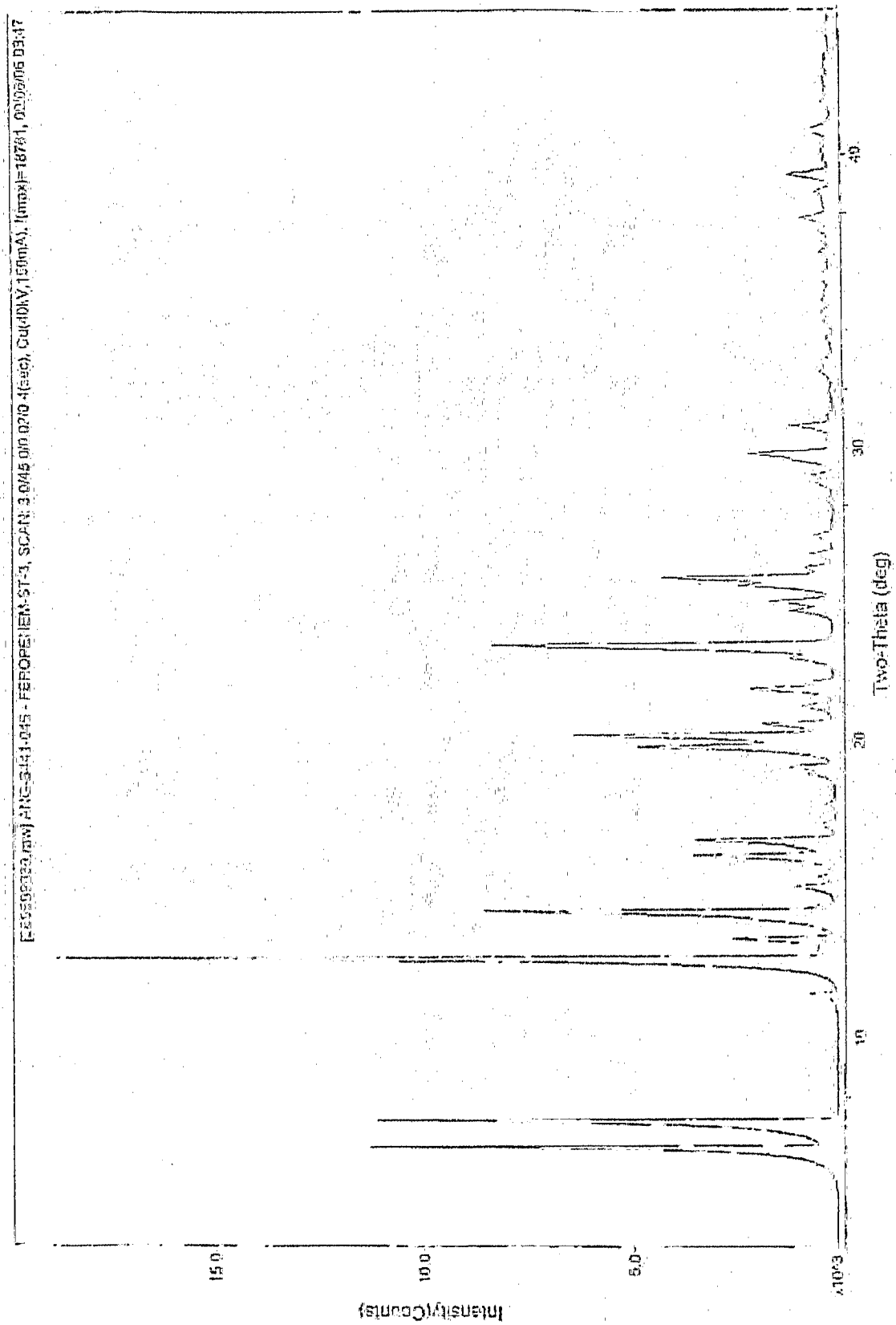


FIGURE-5

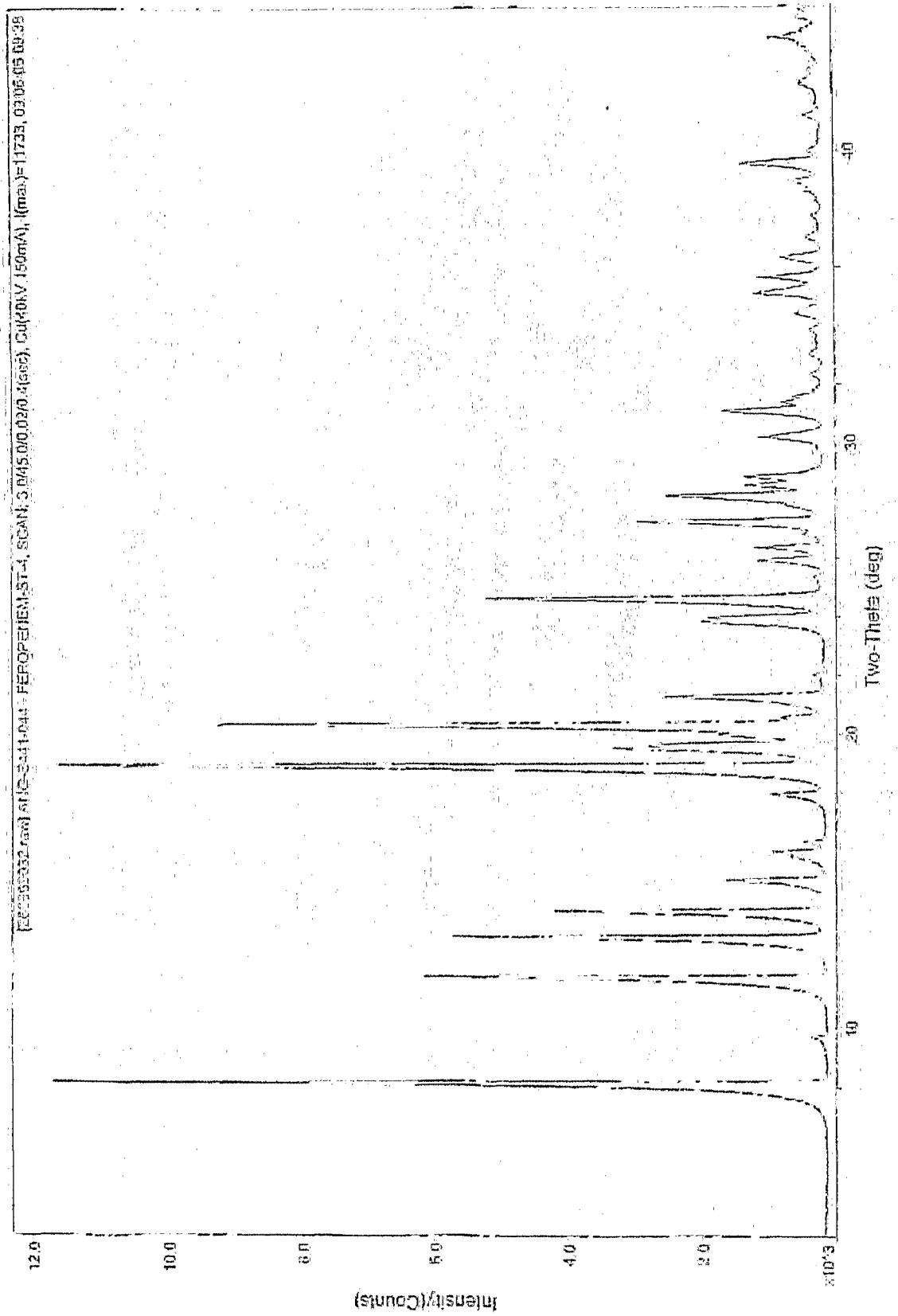

Intensity (Counts)
Two-Theta (deg)
x10^3
12.0
10.0
8.0
6.0
4.0
2.0
10
20
30
40

FIGURE-6

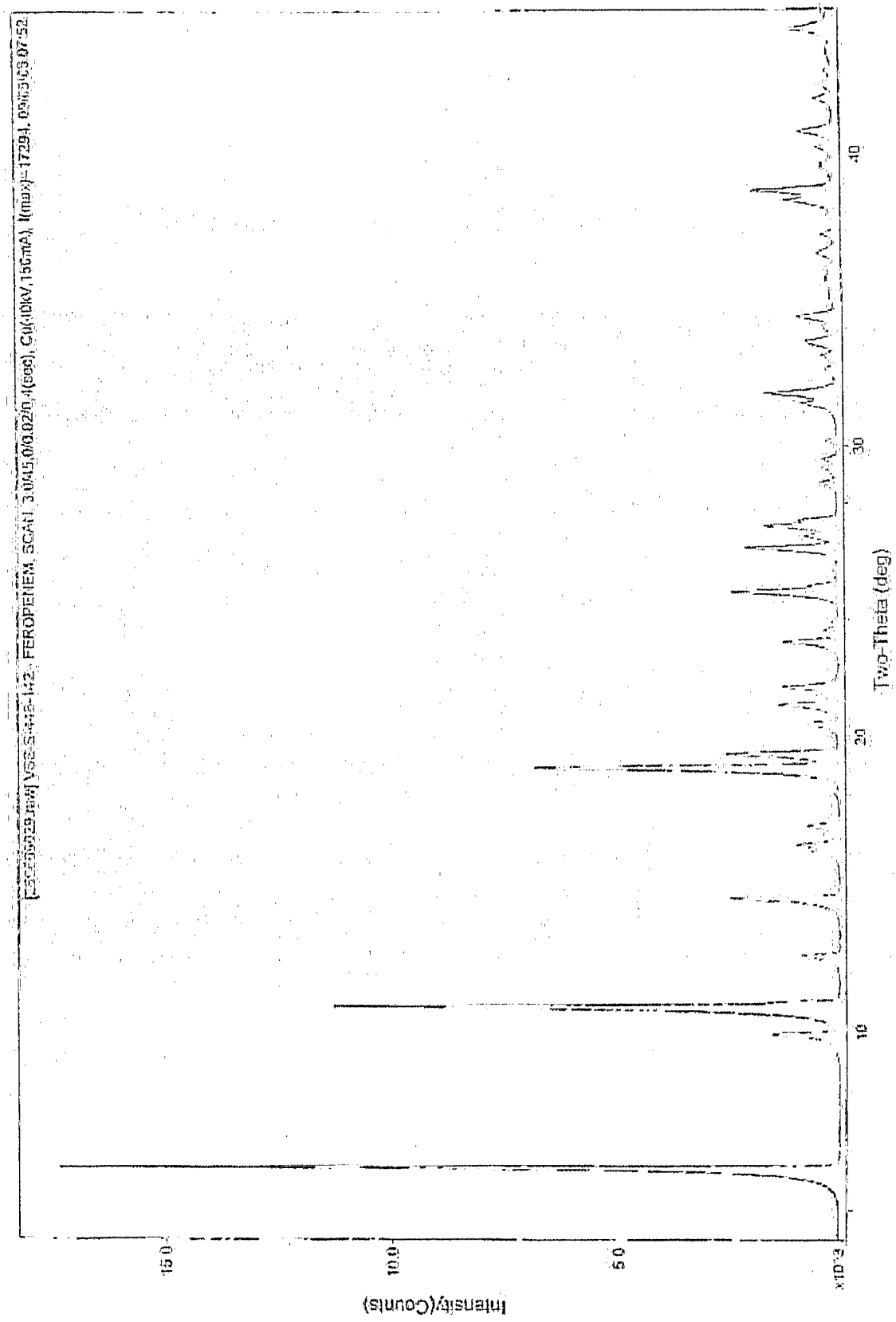


FIGURE : 7

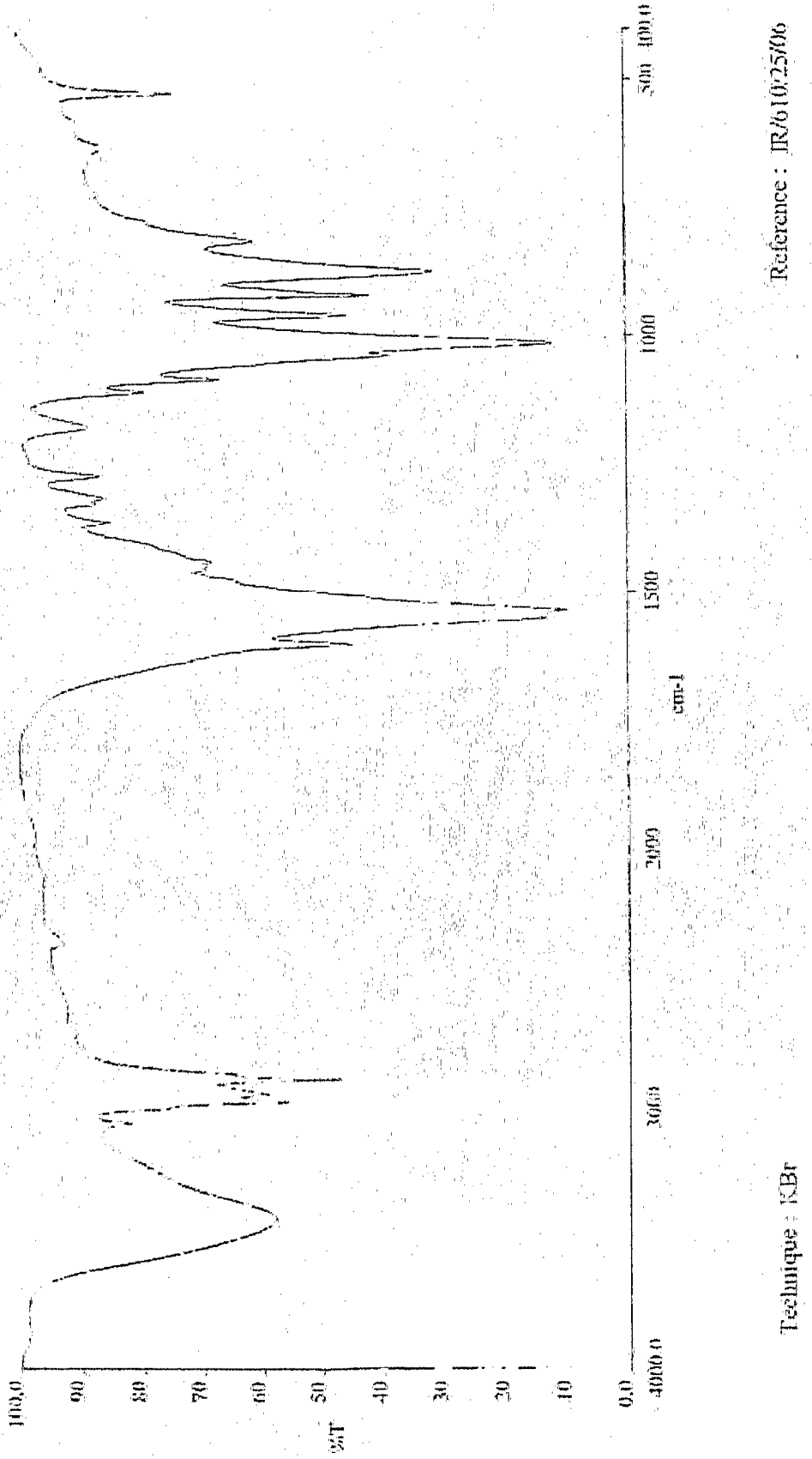

100,0
90
80
70
60
50
40
30
20
10
%T
4000,0
3000
2000
1500
1000
500
400,0
cm-1
Technique : KBr
Reference : IR/61025/06

FIGURE : 8

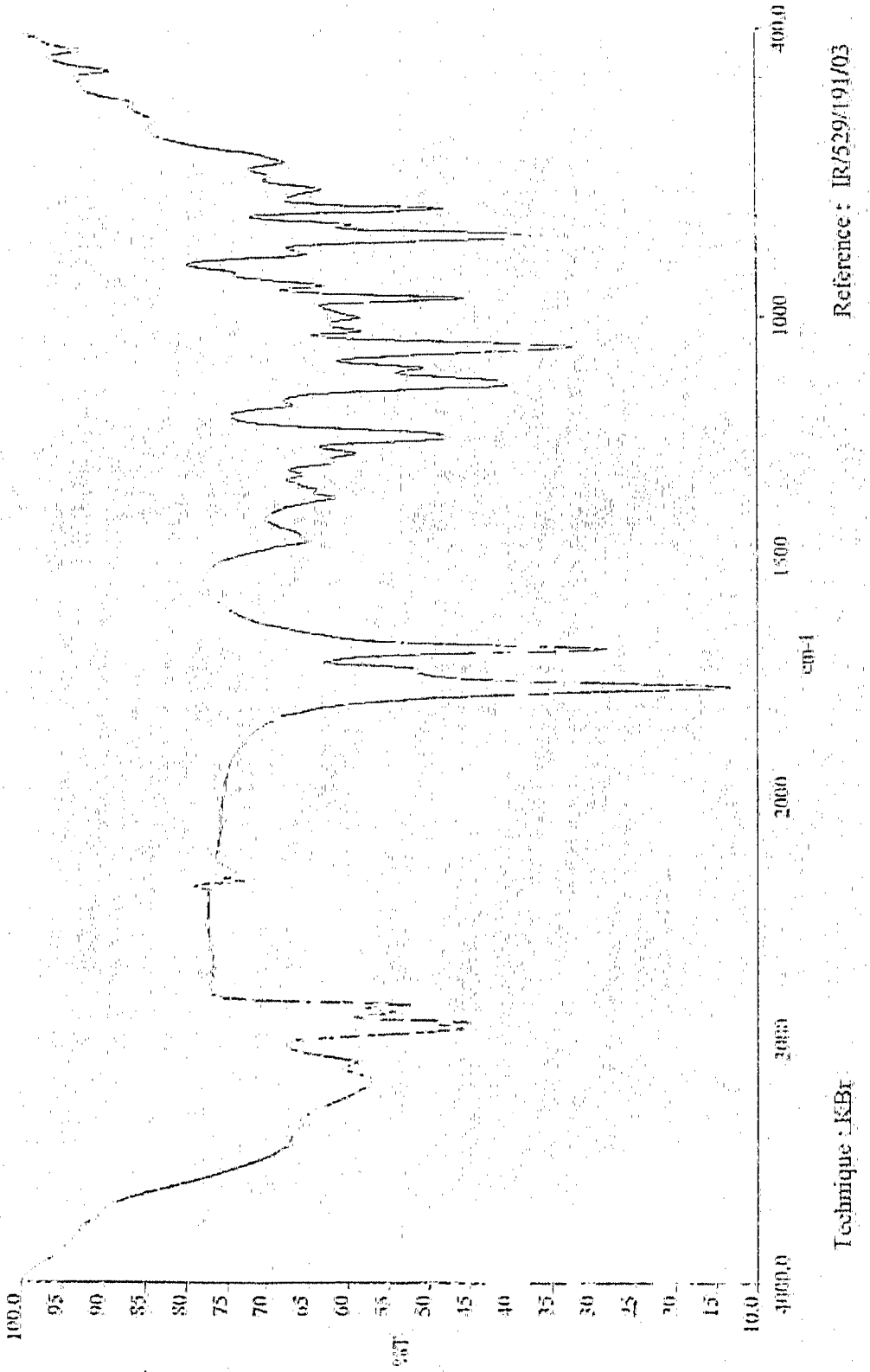

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
Technique : KBr
Reference : IR/529/191/03

FIGURE: 9

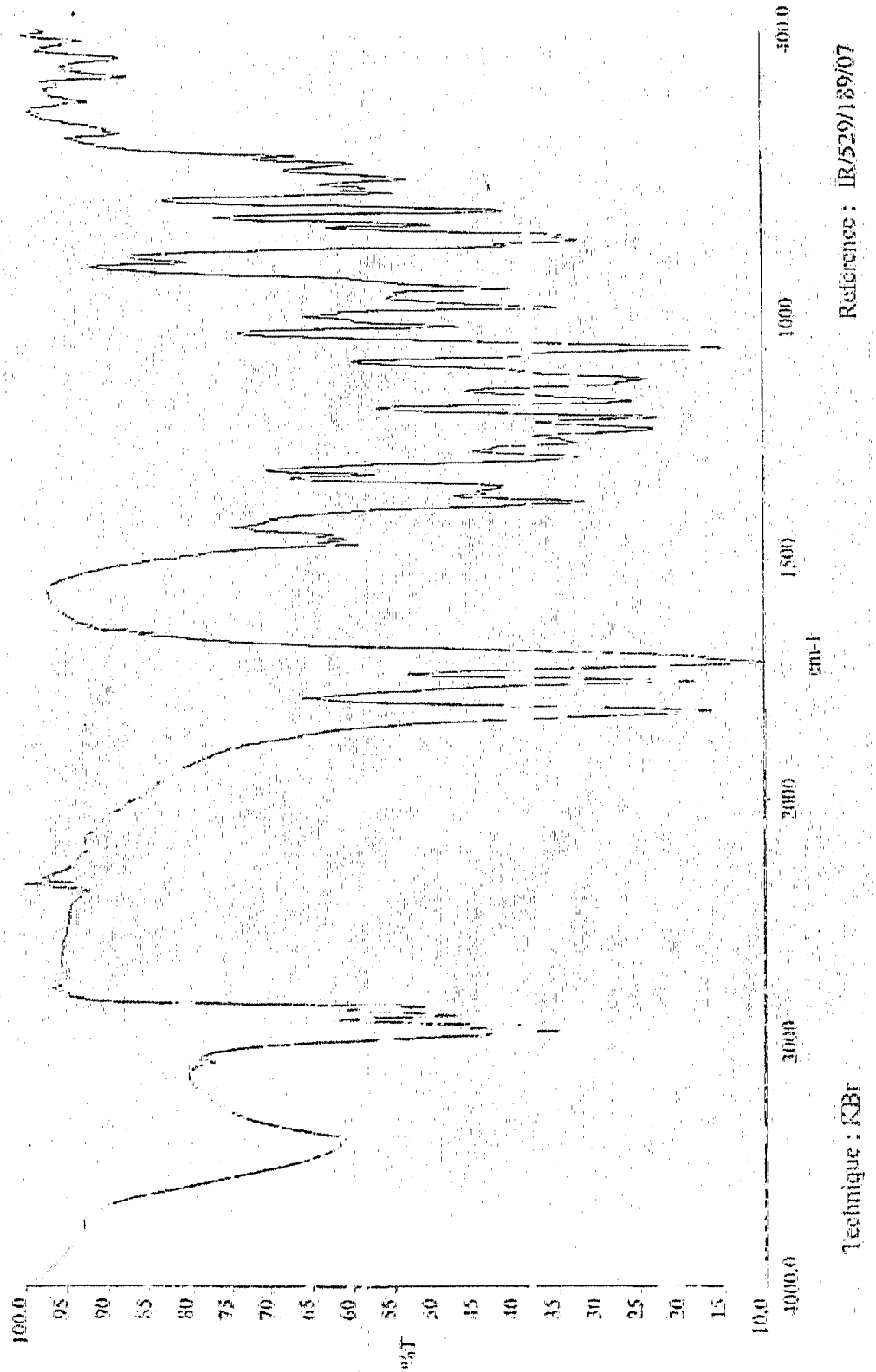

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.0
%T
4000.0
3000
2000
1500
1000
500.0
cm-1
Technique : KBr
Référence : IR/529/189/07

FIGURE : 10

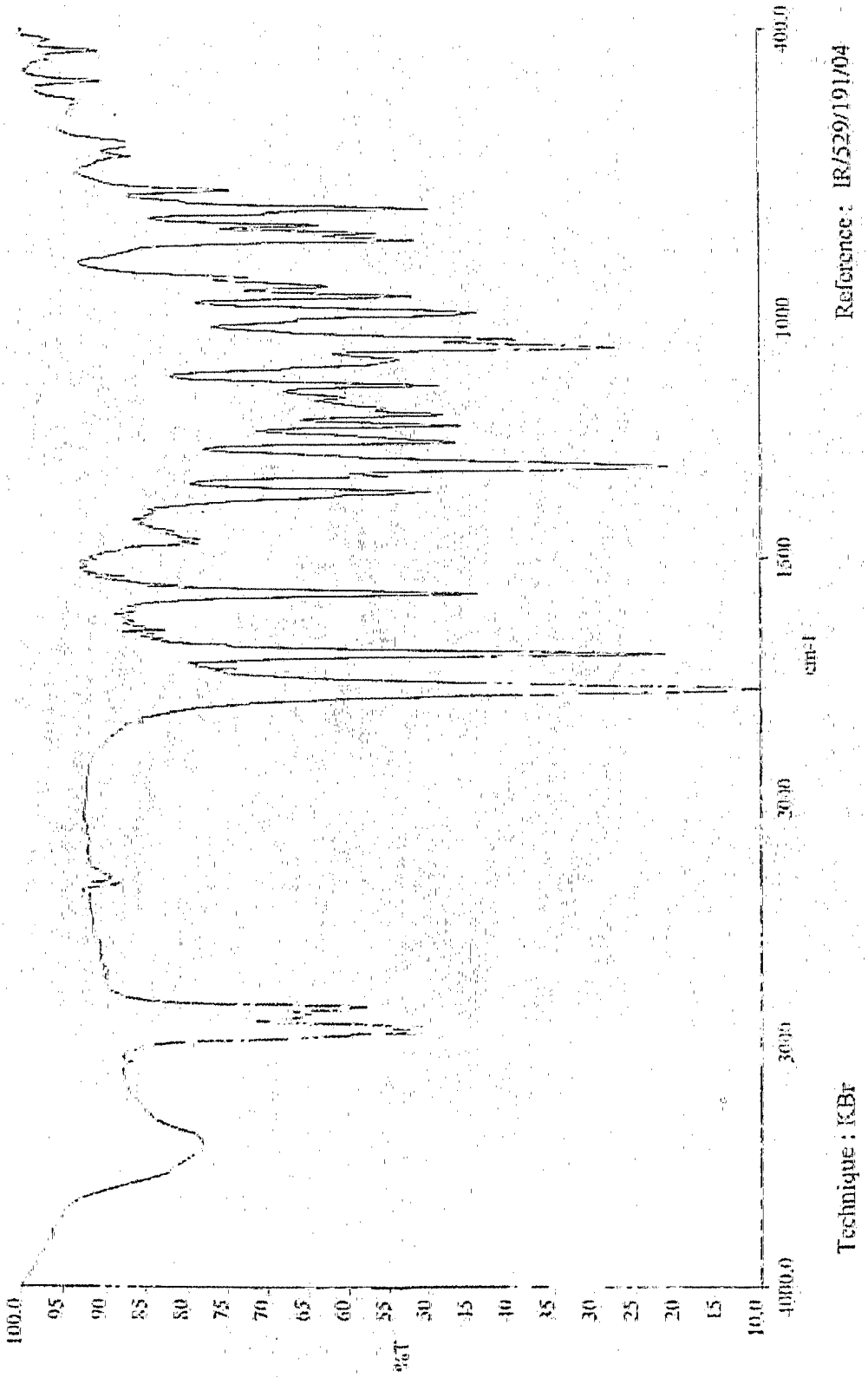

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
Technique : KBr
Reference : IR/529/191/04

FIGURE : 11

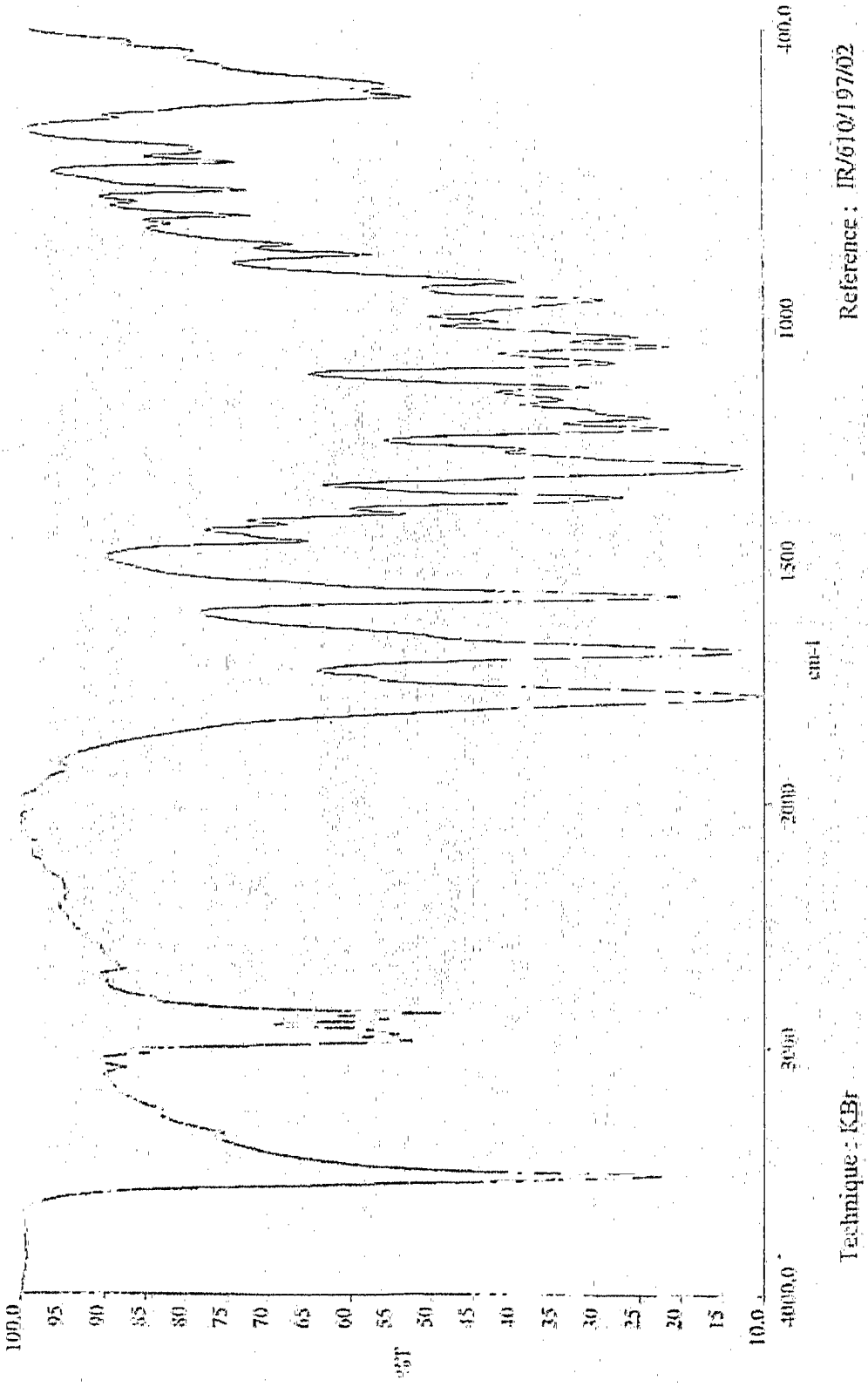
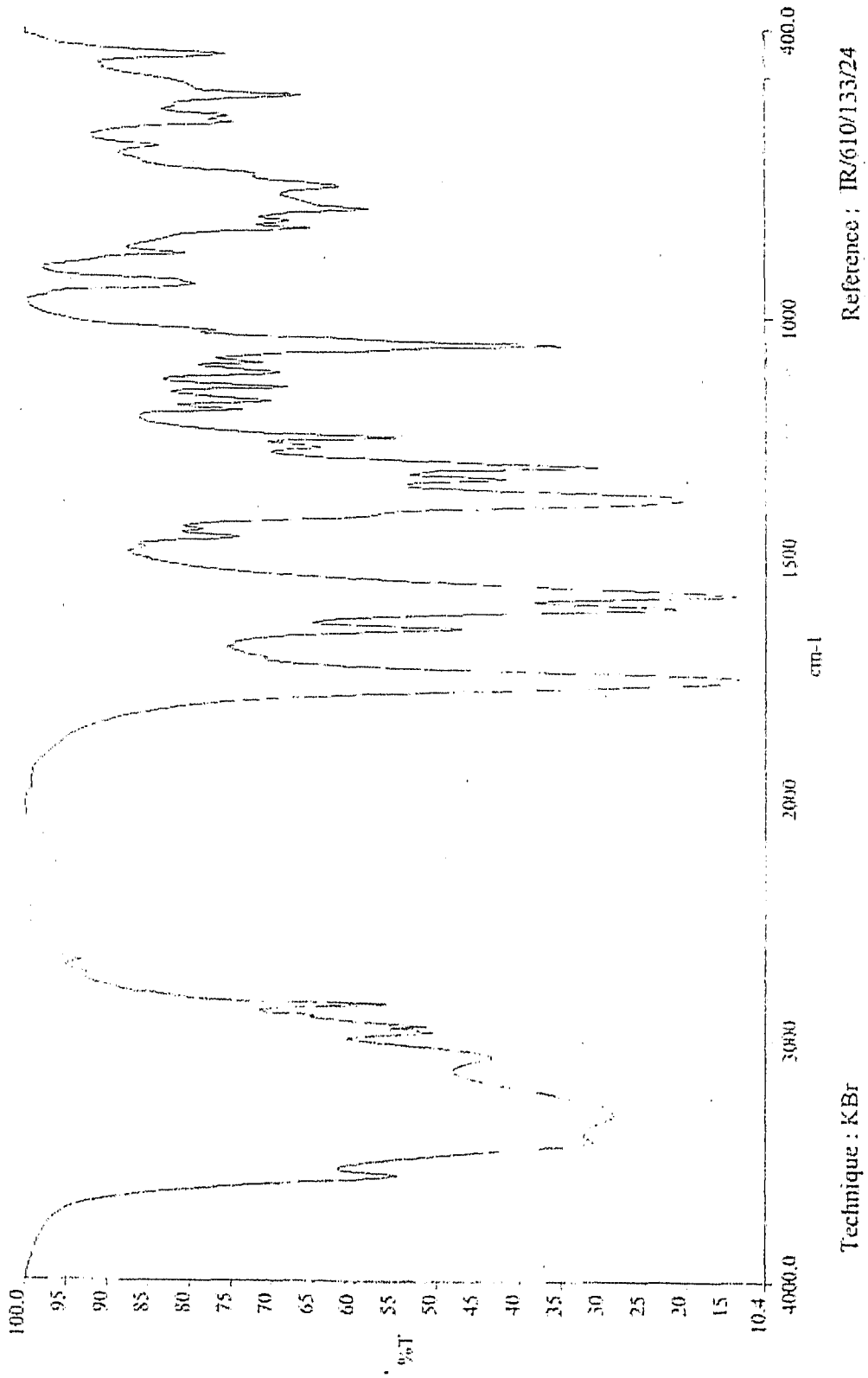

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
Technique : KBr
Reference : IR/610/197/02

FIGURE : 12


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.4
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
Technique : KBr
Reference : IR/610/133/24