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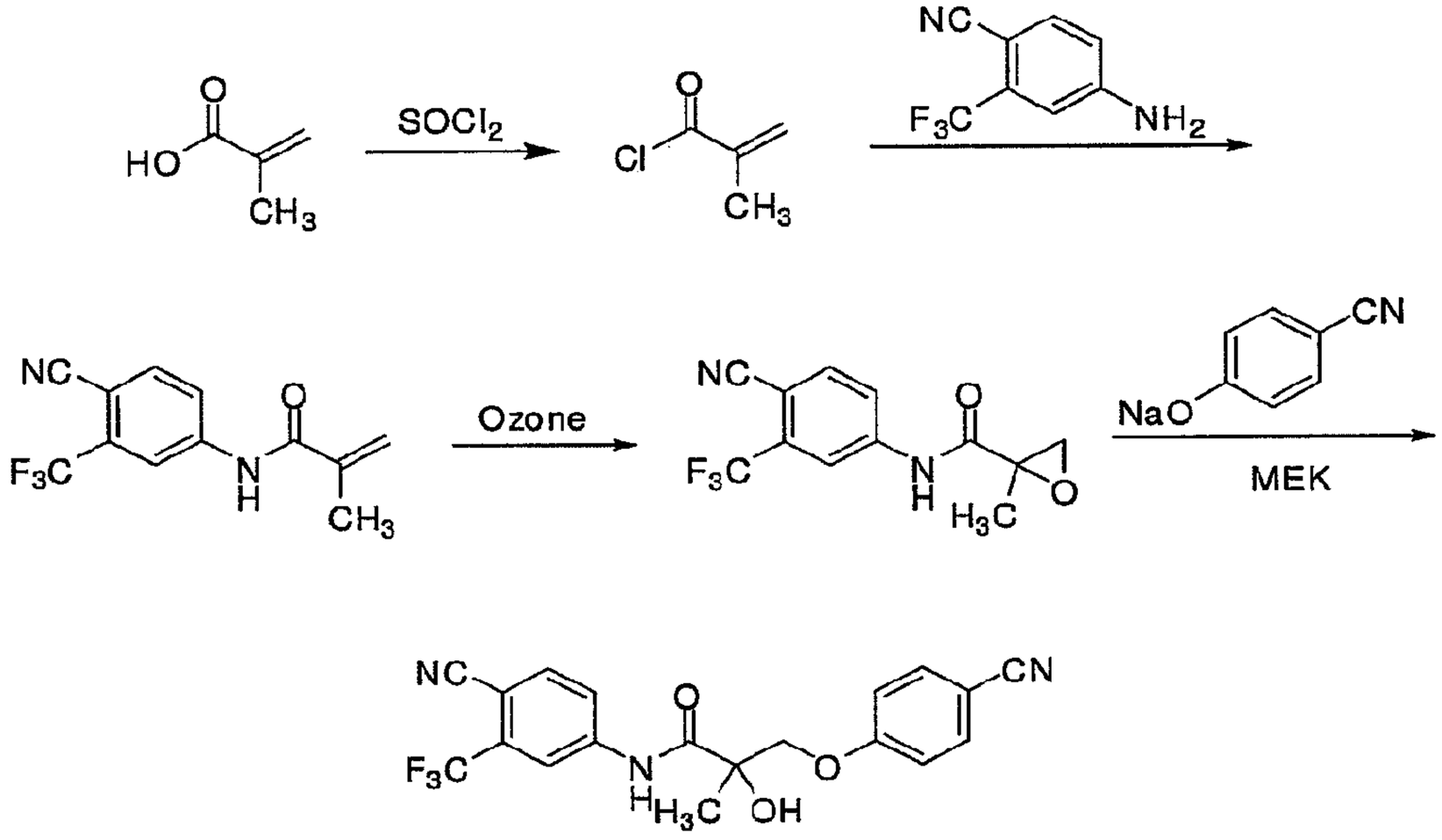
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(54) Titre : FORMES SOLIDES DE MODULATEURS DE RECEPTEUR D'ANDROGENE
(54) Title: SOLID FORMS OF SELECTIVE ANDROGEN RECEPTOR MODULATORS



(57) Abrégé/Abstract:
The present invention relates to a crystalline form of an (R) or (S)-N-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound (form A), characterized by: an X-ray powder diffraction pattern displaying peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 8.6 (10.3), 9.9 (8.9), 12.4 (7.1), 15.0 (5.9), 16.7 (5.3), 17.3 (5.1), 18.0 (4.9), 18.5 (4.8), 19.3 (4.6), 19.8 (4.5), 20.6 (4.3), 21.8 (4.1), 22.3 (4.0), 23.4 (3.8), 23.9 (3.7), 24.6 (3.6), 24.9 (3.6), 25.4 (3.5), 26.0 (3.4), 26.5 (3.4), 27.8 (3.2).

ABSTRACT

The present invention relates to a crystalline form of an (R) or (S)-N-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound (form A), characterized by: an X-ray powder diffraction pattern displaying peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 8.6 (10.3), 9.9 (8.9), 12.4 (7.1), 15.0 (5.9), 16.7 (5.3), 17.3 (5.1), 18.0 (4.9), 18.5 (4.8), 19.3 (4.6), 19.8 (4.5), 20.6 (4.3), 21.8 (4.1), 22.3 (4.0), 23.4 (3.8), 23.9 (3.7), 24.6 (3.6), 24.9 (3.6), 25.4 (3.5), 26.0 (3.4), 26.5 (3.4), 27.8 (3.2).

SOLID FORMS OF SELECTIVE ANDROGEN RECEPTOR MODULATORS

RELATED APPLICATION

[0001] This application is a divisional application of Canadian Patent Application Serial No. 2,709,118 filed September 11, 2008.

FIELD OF INVENTION

[0001a] The present invention relates to a crystalline form of *(R)* or *(S)-N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (form A).

BACKGROUND OF THE INVENTION

[0002] The androgen receptor ("AR") is a ligand-activated transcriptional regulatory protein that mediates induction of male sexual development and function through its activity with endogenous androgens. Androgens are generally known as the male sex hormones. The androgenic hormones are steroids which are produced in the body by the testes and the cortex of the adrenal gland or can be synthesized in the laboratory. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone mass, prostate growth, spermatogenesis, and the male hair pattern (Matsumoto, Endocrinol. Met. Clin. N. Am. 23:857-75 (1994)). The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal steroid secreted by the testes and is the primary circulating androgen found in the plasma of males Testosterone is converted to DHT by the enzyme 5 alpha-reductase in many peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most androgen actions (Zhou, et al., Molec. Endocrinol. 9:208-18 (1995)). Other steroidal androgens include esters of testosterone, such as the cypionate, propionate, phenylpropionate, cyclopentylpropionate, isocarporate, enanthate, and decanoate esters, and other synthetic androgens such as 7-Methyl-Nortestosterone ("MENT") and its acetate ester (Sundaram et al., "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," Ann. Med., 25:199-205 (1993) ("Sundaram"). Because the AR is involved in male sexual development and function, the AR is a likely target for effecting male contraception or other forms of hormone replacement therapy.

[0003] New innovative approaches are urgently needed at both the basic science and clinical levels to develop compounds which are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian

cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

[0004] Polymorphs, solvates and salts of various drugs have been described in the literature as imparting novel properties to the drugs. Organic small drug molecules have a tendency to self-assemble into various polymorphic forms depending on the environment that drives the self assembly. Heat and solvent mediated effects can also lead to changes that transform one polymorphic form into another.

[0005] Identifying which polymorphic form is the most stable under each condition of interest and the processes that lead to changes in the polymorphic form is crucial to the design of the drug manufacturing process in order to ensure that the final product is in its preferred polymorphic form. Different polymorphic forms of an active pharmaceutical ingredient (API) can lead to changes in the drug's solubility, dissolution rate, pharmacokinetics and ultimately its bioavailability and efficacy in patients.

SUMMARY OF THE INVENTION

[0006] In one embodiment, the present invention relates to crystalline form of *(R)* or *(S)-N*-(4-cyano-3-(trifluoromethyl)pheny1)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound (form A). In some embodiments such compounds are useful for their androgenic and anabolic activity. *(R)* or *(S)- N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide are selective androgen receptor modulators (SARMs) useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM); c) treatment of conditions associated with Androgen Decline in Female (ADIF); d) treatment and/or prevention of chronic muscular wasting; and/or; e) decreasing the incidence of, halting or causing a regression of prostate cancer; f) oral androgen replacement and/or other clinical therapeutic and/or diagnostic areas.

[0007] In one embodiment the present invention provides a crystalline form of an (R) or (S)-N-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound (form A), characterized by: an X-ray powder diffraction pattern displaying peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 8.6 (10.3), 9.9 (8.9), 12.4 (7.1), 15.0 (5.9), 16.7 (5.3), 17.3 (5.1), 18.0 (4.9), 18.5 (4.8), 19.3 (4.6), 19.8 (4.5), 20.6 (4.3), 21.8 (4.1), 22.3 (4.0), 23.4 (3.8), 23.9 (3.7), 24.6 (3.6), 24.9 (3.6), 25.4 (3.5), 26.0 (3.4), 26.5 (3.4), 27.8 (3.2).

[0008] In one embodiment the present invention provides, an anhydrous crystalline form of *(R)* or *(S)-N*-(4-cyano-3-(trifluoromethyflphenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[0009] In another embodiment this invention provides, a composition comprising a therapeutic amount of crystalline form of an anhydrous crystalline form of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[00010] In one embodiment this invention provides, a process for the preparation of a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide said process comprising dissolving (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in at least one organic solvent at a temperature of between about -20 °C to +5 °C under conditions permissive to crystallization, thereby obtaining said crystalline form.

[00011] In one embodiment, this invention provides, a paracrystalline (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00012] In another embodiment, this invention provides, a composition comprising paracrystalline form of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[00013] In one embodiment, this invention provides, a process for the preparation of paracrystalline (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising stirring a suspension of a crystalline form of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in water at ambient temperature of about 20-30 °C for at least 0.5 hours, to obtain a paracrystalline compound.

[00014] In one embodiment this invention provides, a composition comprising a mixture of crystalline and paracrystalline solid forms of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound and a suitable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

[00015] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[00016] **Fig. 1** schematically depicts the synthesis of racemic mixtures of compound **1**.

[00017] **Fig. 2** schematically depicts the synthesis of the (*S*)-enantiomer of compound **S-1**.

[00018] **Fig. 3** schematically depicts the synthesis of the (*R*)-enantiomer of compound **R-1**.

[00019] **Fig. 4A - 4D** depict XRPD patterns for solid forms of Compound **S-1.** **4A**-solid form A-batch P1 of compound **S-1**; **4B**-solid form A-batch P2 of compound **S-1**; **4C**-solid form A-batch P3 of compound **S-1**; **4D**-solid form B'-batch P4 of compound **S-1**.

[00020] **Fig. 5A - 5D** are Raman spectra of sample batches P1-P4 of compound **S-1**, respectively. The laser power setting was 100 mW, at a resolution of 2 cm^{-1}.

[00021] **Fig. 6A- 6D** are TG-FTIR spectra of sample batches P1-P4 of compound **S-1**, respectively. Conditions included a temperature range operation in the dynamic mode of 25 °C/10.0/250 °C, in an N_2 atmosphere.

[00022] **Fig. 7A - 7D** are DSC spectra of sample batches P1-P4 of compound **S-1**, respectively. The asterisk indicates a settling effect, an artifact of the machinery used.

[00023] **Fig. 8A, 8B and 8C**, are SEM micrographs of sample batches P1, P2 and P4 of compound **S-1**, respectively.

[00024] **Fig. 9A, 9B and 9C**, are Dynamic Vapor Sorption (DVS) spectra of sample batches, P1, P2, and P4 of compound **S-1**, respectively. **9A** is a DVS of form A. **9B** is a DVS of form A. **9C** is a DVS of form B'.

[00025] **Fig. 10** demonstrates XRPD spectra of the compound obtained after varying the **S-1** concentration in given solvents, varying the solvents, or a combination thereof. **A**- demonstrates XRPD spectra after compound **S-1**, Form A, suspended in *n*-heptane, 108 mg/2.0 mL. **B**-demonstrates XRPD spectra after compound **S-1**, Form B', suspended in ethyl acetate +*n*-heptane 1:2 (v/v), 81mg/1.7mL. **C**-demonstrates XRPD spectra after compound **S-1**, Form B' suspended in ethyl acetate +*n*-pentane 1:2 (v/v), 101 mg/1.0mL. **D**- demonstrates XRPD spectra after compound **S-1** Form A, suspended in ethyl acetate +*n*-pentane 1:2 (v/v), 128 mg /2.0 mL. **E**-demonstrates XRPD spectra after compound **S-1** Form A, suspended in ethyl acetate +*n*-pentane 1:2 (v/v), 112 mg /2.0 mL. **F**- demonstrates XRPD spectra after compound **S-1** Form A, suspended in methyl acetate +*n*-pentane 1:2 (v/v), 126 mg /2.0 mL.

[00026] **Fig. 11** shows the XRPD pattern representing the results of vapor diffusion experiments conducted with compound **S-1. A**- demonstrates XRPD spectra of compound **S-1** in toluene and *n*-hexane at 23 °C for 2 days. **B** -shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 11A. **C**- demonstrates XRPD spectra obtained for compound **S-1** in acetic acid and water at 23 °C for 7 days. **D**- shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 11B.

[00027] **Fig. 12** shows the XRPD pattern representing the results of evaporation experiment wherein solutions of compounds were dried at room temperature (dry N_2 flow) without stirring. **12A**- demonstrates XRPD pattern obtained of compound **S-1** (batch P1) in ethyl-acetate solution. **12B**- demonstrates a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD

obtained in Fig 12A. **12C**- demonstrates XRPD pattern obtained of compound **S-1** (batch P1) from THF, to provide form C. **12D** -demonstrate XRPD patterns of a mixture of form A (red, top) and form C (blue, bottom), as presented in Fig. 12C.

[00028] **Fig. 13** shows the XRPD spectra representing the results of recrystallization from solution experiment wherein compound **S-1** was dissolved in different solvent system at room temperature and cooled to +5 °C or to -20 °C. **13A**- demonstrates XRPD spectra obtained of compound **S-1** (batch P1) in ethylacetate+*n*-heptane 1:1 (v/v). **13B** - shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 13A. **13C**- demonstrates XRPD spectra obtained of compound **S-1** (batch P1) in acetonitrile +toluene 1:3 v/v. **13D**- shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 13B.

[00029] **Fig. 14** shows the XRPD spectra representing the results of freeze drying experiment. **14A-** demonstrates XRPD spectra obtained of compound **S-1** (batch P-1) in 1-4-dioxane and cooled to -50°C. **14B** - shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 14A.

[00030] **Fig. 15** demonstrates a DSC thermogram representing the results of a drying experiment when compound **S-1** (batch P4) was dried overnight in a dry N_2 atmosphere. The asterisk indicates a settling effect, an artifact of the machinery used.

[00031] **Fig. 16** demonstrates XRPD spectra representing the results of relative stability experiments wherein suspension experiments were carried out with mixtures of batches of **S-1**. **16A**- demonstrates XRPD spectra obtained from a mixture of batches of compound **S-1** (P1, P18, P24, P30, P37 and P38, all batches have a XRPD characteristics of Form A) in ethylacetate+*n*-heptane 1:2 (v/v) 130 mg/2.0 mL. **16B** shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 16A. **16C**- demonstrates XRPD spectra obtained from a mixture of batches of compound **S-1** (P1 and P52 where batch P1 is Form A and P52 is Form A+C) in ethylacetate+*n*-heptane 1:2 (v/v); (81+64) mg/2.0 mL. 16**D** shows a superimposed spectra of XRPD of batch P1 (Form A) and the XRPD obtained in Fig 16B.

[00032] Fig. 17 provides a DSC thermogram and XRPD pattern, representing the results of water vapor sorption where S-1 (batch P1) was stored in a glass tube under 96% r.h (relative humidity) at room temperature. **17A**- demonstrates the DSC results obtained for compound S-1 batch P1 with no solvent after 11 weeks. **17B**- demonstrates XRPD of compound S-1 batch P1 (form A) in water after 19 h at 37 °C, resulting in formation of form B'. **17C**- demonstrates XRPD of compound S-1 batch P1 (form A) in acetic acid+water 1:2 (v/v) after 20 h at 23 °C. **17D**- shows a DSC thermogram of heating a sample of form A (black), cooling of the sample after melting (grey) and reheating of the sample (white). Heating rates were 10°C/min while the cooling rate was 1°C/min. Heating form A beyond the melting temperature produces B" which doesn't revert

to A even when the sample is cooled back down to ambient temperature. **17E**- 1°C/min DSC runs of form A (grey), B" (black), mixture of A and D (white) and mixture of B" and D (dark grey). A and B" can undergo crystallization to D but only in the presence of D to act as seeds for crystallization.**17F**- DSC graphs for form A stored at ambient temperature/100%RH for 7 days (light grey), 50°C/0%RH for 7 days (dark grey), and 50°C/75%RH for 6 hours (white) along with the DSC graph of the original sample (black). **17G**- (a) DSC graphs of polymorph A seeded with form D and stored at 50°C/75%RH. (b) DSC graphs of form A seeded with form D and stored at 50°C in water.

[00033] **Fig. 18** demonstrates XRPD patterns of a superimposed spectra of XRPD of form A (top) and form D (bottom) of compound **S-1**.

[00034] **Fig 19** demonstrates a DSC thermograms of forms A and D.

[00035] **Fig 20** Thermogravimetric analysis (TGA) graph of the toluene solvate (red) and form D (black).

DETAILED DESCRIPTION OF THE INVENTION

[00036] In some embodiments, the present invention provides solid forms of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and processes of preparation of the same. This invention also provides pharmaceutical compositions comprising the solid forms of (*R*) or (*S*)- *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methyl propanamide, and uses thereof.

[00037] (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide are androgen receptor targeting agents (ARTA), which demonstrate androgenic and anabolic activity. In some embodiments, the methyl propionamides as herein described are selective androgen receptor modulators (SARM), which in some embodiments are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of chronic muscular wasting; e) decreasing the incidence of, halting or causing a regression of prostate cancer; f) oral androgen relacement and/or other clinical therapeutic and/or diagnostic areas.

[00038] In some embodiments, this invention provides polymorphic solid forms of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compounds of this invention. In one embodiment the term "polymorph" refers to a specific form of the SARM compounds of this invention, for example, polymorphs may represent crystalline forms that can vary in pharmaceutically relevant physical properties between one form and another, for example under different crystallization conditions, environmental conditions, hygroscopic activity of the compounds, etc.

[00039] In one embodiment, this invention provides, a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00040] In one embodiment, this invention provides, a crystalline form of anhydrous *(R)* or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00041] In one embodiment, this invention provides, a crystalline form of anhydrous (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00042] In another embodiment, the crystalline form of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (compound **S-1**), is characterized by:

a. an X-Ray Powder diffraction pattern comprising peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 8.6 (10.3), 9.9 (8.9), 12.4 (7.1), 15.0 (5.9), 16.7 (5.3), 17.3 (5.1), 18.0 (4.9), 18.5 (4.8), 19.3 (4.6), 19.8 (4.5), 20.6 (4.3), 21.8 (4.1), 22.3 (4.0), 23.4 (3.8), 23.9 (3.7), 24.6 (3.6), 24.9 (3.6), 25.4 (3.5), 26.0 (3.4), 26.5 (3.4), 27.8 (3.2);and

b. a melting point of about 80 °C.

[00043] According to this aspect and in another embodiment, such a crystalline form of compound **S-1**, having all or part of the characteristics listed in (a) and (b) is referred to herein as crystalline Form A.

[00044] In another embodiment, the solubility of Form A in water is between 20-30 mg/L at 22 °C. In another embodiment, the solubility of Form A in water is between 23-27 mg/L at 22 °C.

[00045] In one embodiment, this invention provides a crystalline form of an (*R*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (compound **R-1**), wherein said crystalline form is obtained by methods similar to that of the *S* isomer, as described herein. In some embodiments, such a crystalline form of compound **R-1**, is structurally related and/or possesses similar characteristics to that of compound **S-1**.

[00046] In one embodiment this invention provides a paracrystalline (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00047] In one embodiment this invention provides a paracrystalline (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound.

[00048] In one embodiment, the paracrystalline form of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (compound **S-1**) is characterized by:

a. an X-Ray Powder diffraction pattern displaying a broad halo with two harmonic peaks between 15-25 °2θ and

b. a glass transition point of about 55 °C.

[00049] According to this aspect and in another embodiment, such a paracrystalline form of compound **S-1**, having all or part of the characteristics listed in (a) and (b) is referred herein as paracrystalline form B'.

[00050] In one embodiment the term "paracrystalline" refers to the state of material exhibiting short-range order without long-range order such as liquid crystals or other type of lamellar structures. In one embodiment, the paracrystalline form is a liquid crystal. In another embodiment, the Form B' of compound **S-1** is a paracrystalline. In another embodiment, form A of **S-1** may convert in whole or in part to paracrystalline Form B' of **S-1**.

[00051] In another embodiment, the solubility of Form B' in water is between 20-30 mg/L at 22 °C. In another embodiment, the solubility of Form B' in water is between 23-27 mg/L at 22 °C.

[00052] In one embodiment, this invention provides an paracrystalline form B'' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide, characterized by:

a. an X-Ray Powder diffraction pattern displaying a broad halo with two harmonic peaks between 15-25 °2θ and

b. a glass transition point of about 55 °C.

[00053] In one embodiment, this invention provides a crystalline Form C of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide characterized by:

a. an X-Ray Powder diffraction pattern comprising unique peaks at °2θ (d value Å) angles of about 6.9 (12.8), 9.5 (9.3), 13.5 (6.6), 16.0 (5.6), 22.8 (3.9).

[00054] In another embodiment, crystalline Form C of compound **S-1** is obtained as a mixture of Form A and C, by evaporating A out of THF.

[00055] In one embodiment, this invention provides a crystalline Form D of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide characterized by:

a. an X-Ray powder diffraction pattern comprising unique peaks at °2θ (d value Å) angles of about 4.4 (19.9), 8.5 (10.4), 8.8 (10.0), 11.3 (7.8), 12.7 (6.9), 13.8 (6.4), 14.4 (6.1), 14.6 (6.0), 15.1 (5.8), 16.1 (5.5), 16.6 (5.3), 16.9 (5.2), 18.0 (4.9), 18.7 (4.7), 19.0 (4.6), 19.4 (4.55), 20.8 (4.25), 22.1 (4.0), 22.7 (3.9), 23.1 (3.8), 23.4 (3.8), 24.7 (3.6), 24.9 (3.56), 25.3 (3.51), 27.8 (3.2), 29.3 (3.0); and ,

b. a melting point of about 130 °C.

[00056] In another embodiment, crystalline Form D of compound **S-1** is stable at 50°C/75%RH (Relative Humidity) as well as the other conditions of ambient/75%RH, ambient/100%RH, 30°C/75%RH and 50°C/0%RH.

[00057] In another embodiment the characteristics of the different solid forms of **S-1** are presented in Example 2 and Figures 4-20.

[00058] Solid forms of this invention can be analysed by any method known in the art for example and in one embodiment, X-ray powder diffraction. In another embodiment analysis of the solid forms of this invention may comprise Raman Spectroscopy. In another embodiment analysis of the solid forms of this invention may comprise TG-FTIR (thermo gravimetric fourier transform infrared). In another embodiment analysis of the solid forms of this invention may comprise FT-Raman (fourier transform-Raman). In another embodiment analysis of the solid forms of this invention may comprise DSC (differential scanning calorimetry). In another embodiment analysis of the solid forms of this invention may comprise DVS (dynamic vapor sorption). In another embodiment analysis of the solid forms of this invention may comprise SEM (Scanning electron microscopy).

[00059] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and B' in a ratio of between about 95:5 to 85:15, respectively. In another embodiment, the ratio is between about 85:15 to 75:25, respectively. In another embodiment, the ratio is between about 75:25 to 65:35, respectively. In another embodiment, the ratio is between about 95:5 to 90:10, respectively. In another embodiment, the ratio is between about 90:10 to 85:15, respectively. In another embodiment, the ratio is between about 97:3 to 93:7, respectively. In another embodiment, the ratio is between about 85:15 to 80:20. In another embodiment, the ratio is between about 70:20 to 60:20. In another embodiment, the ratio is 50:50, respectively.

[00060] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, B' and C in a ratio of between about 90:5:5 to 80:10:10, respectively. In another embodiment, the ratio is between about 80:10:10 to 75:15:10, respectively. In another embodiment, the ratio is between about 95:3:2 to 90:7:3, respectively. In another embodiment, the

ratio is between about 75:15:10 to 65:20:15. In another embodiment, the ratio is between about 70:20:10 to 60:20:20.

[00061] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, B' and D in a ratio of between about 5:5:90 to 10:10:80, respectively. In another embodiment, the ratio is between about 10:10:80 to 10:15:75, respectively. In another embodiment, the ratio is between about 2:3:95 to 3:7:90, respectively. In another embodiment, the ratio is between about 10:15:75 to 15:20:65. In another embodiment, the ratio is between about 10:20:70 to 20:20:60.

[00062] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and C in a ratio of between about 98:2 to 95:5, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and C in a ratio of between about 95:5 to 90:10, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and C in a ratio of between about 90:10 to 85:15, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, and C in a ratio of between about 85:15 to 80:20, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, and C in a ratio of about 50:50, respectively.

[00063] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and D in a ratio of between about 2:98 to 5:95, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and D in a ratio of between about 5:95 to 10:90, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A and D in a ratio of between about 10:90 to 15:85, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, and D in a ratio of between about 15:85 to 20:80, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms A, and D in a ratio of about 50:50, respectively.

[00064] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and D in a ratio of between about 2:98 to 5:95, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and D in a ratio of between about 5:95 to 10:90, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and D in a ratio of between about 10:90 to 15:85, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B', and D in a ratio of between about 15:85 to 20:80, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B', and D in a ratio of about 50:50, respectively.

[00065] In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and C in a ratio of between about 98:2 to 95:5, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and C in a ratio of between about 95:5 to 90:10, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and C in a ratio of between about 90:10 to 85:15, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and C in a ratio of between about 85:15 to 80:20, respectively. In one embodiment, this invention provides a polymorphic mixture comprising crystalline forms B' and C in a ratio of about 50:50, respectively.

[00066] In another embodiment, the ratio between crystalline form A to crystalline form B' is between about 95:5 to 85:15. In another embodiment, the ratio between crystalline form A to crystalline form B' is between about 98:2 to 95:5. In another embodiment, the ratio between crystalline form A to crystalline form B' is between about 85:15 to 75:25. In another embodiment, the ratio between crystalline form A to crystalline form B' is between about 75:25 to 65:35 respectively.

[00067] In one embodiment a sample of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide may comprise a mixture of solid form A, B', B'', C and D. In another embodiment the percentage of several solid forms in a sample (for example the percentage of solid form A and B in a sample) can be determined by running a Modulated DSC (Differential Scanning Calorimetry) at a heating rate of 3 °C/min. from 10 °C to 130 °C, followed by linear integration of the solid form A and/or solid form B to obtain the enthalpy of each.

[00068] In one embodiment the solid form of a SARM compound can influence its bioavailability, stability, processability and ease of manufacture and uses thereof are to be considered part of this invention.

[00069] In one embodiment, this invention provides a process for the preparation of a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising dissolving amorphous (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in at least one organic solvent at a temperature of between about -20 °C to +30 °C under conditions permissive to crystallization, thereby obtaining the crystalline form.

[00070] In one embodiment, this invention provides a process for the preparation of a crystalline form A of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising dissolving amorphous (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in at least one organic solvent at a

temperature of between about -20 °C to +30 °C under conditions permissive to crystallization, thereby obtaining the crystalline form.

[00071] In another embodiment, the temperature for crystallization of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide, is about 5 °C. In another embodiment, the temperature is of about -20 °C. In another embodiment, the temperature is of about 20 °C. In another embodiment, the temperature is between about 20 to 50 °C. In another embodiment, the temperature is about -10 to 0 °C. In another embodiment, the temperature is about 0 to 5 °C. In another embodiment, the temperature is about -10 to -20 °C.

[00072] In another embodiment, form A of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (compound S-1) is prepared by crystallization from an organic solvent comprising a mixture of solvents. In another embodiment the mixture comprises two solvents in a 1:2 v/v ratio, respectively. In another embodiment the mixture comprises two solvents in a 1:3 v/v ratio, respectively. In another embodiment the mixture comprises two solvents in a 1:4 v/v ratio, respectively. In another embodiment the mixture comprises ethyl formate and pentane in a 1:2 v/v ratio, respectively. In another embodiment, the mixture comprises methyl acetate and pentane in a 1:2 v/v ratio, respectively. In another embodiment the mixture comprises ethylacetate and *n*-hexane. In another embodiment the mixture comprises toluene and *n*-hexane. In another embodiment the mixture comprises dichloromethane and *n*-hexane. In another embodiment the mixture comprises acetic acid and water in a 1:2 v/v ratio. In another embodiment, form A is prepared by crystallization from a solvent/antisolvent mixture at ambient temperature. In another embodiment, ethyl acetate, ethanol, dichloromethane or acetonitrile are the solvents and *n*-hexane, *n*-pentane, *n*-heptane and cyclohexane etc. are used as antisolvents. In another embodiment the solvent/antisolvent ratios are between 1:2 and 1:3.

[00073] In another embodiment, the crystalline form A of compound **S-1** is prepared by forming a suspension of a paracrystalline form of compound of formula **S-1** in a solvent/antisolvent mixture. In another embodiment solid form A is prepared by forming a suspension of a paracrystalline form of compound of formula **S-1** in ethylacetate and heptane mixture in a 1:2 v/v ratio, respectively. In another embodiment, solid form A is prepared by forming a suspension of a paracrystalline form of compound of formula **S-1** in a mixture of ethylacetate and pentane in a 1:2 v/v ratio, respectively. In another embodiment, the crystalline form A of compound **S-1** is prepared by forming a suspension of form B' in a solvent/antisolvent mixture at concentrations above the saturation limit at 23°C for several hours followed by drying to obtain form A.

[00074] In another embodiment, form D of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide (compound S-1) is prepared by crystallization from solvent/antisolvent mixture at 50°C using ethyl acetate and cyclohexane as the solvent and

antisolvents, respectively. In another embodiment, form D is prepared from other polymorphic forms by "seeding" the sample with a small amount of D and storing it at 110°C/0%RH for 7 days or at 50°C in water for 24 hours followed by drying. In another embodiment, heating forms A and/or B" to 110°C in the presence of D causes the A and B" forms to rearrange into form D. In another embodiment, form D in the presence of moisture acts as the seed for the crystallization process and drives the transformation of forms A and B' into D.

[00075] In another embodiment, Figure **17G** shows the time evolution of polymorph A seeded with a small amount of D at 50°C/75%RH. The amount of polymorph D initially added to the sample is very small that it isn't detectable by the DSC with heating rate of 10°C/min. After 24 hours, most of the polymorph form A has been converted to B' but a small amount of sample has also been converted to D and the amount of sample in D increases over time. The transformation process is speeded up in Figure 17G by storing the sample in water at 50°C. Form A has been converted to both B' and D after 6 hours but the sample is predominantly in form D by 24 hours.

[00076] In one embodiment this invention provides a process for the preparation of paracrystalline (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising stirring a suspension of a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in water at ambient temperature of about 20-30 °C for at least 0.5 hours, to obtain a paracrystalline compound.

[00077] In one embodiment this invention provides a process for the preparation of paracrystalline form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising stirring a suspension of a crystalline form of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in water at ambient temperature of about 20-30 °C for at least 0.5 hours, to obtain a a paracrystalline compound.

[00078] In one embodiment this invention provides a process for the preparation of paracrystalline form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising stirring a suspension of a crystalline form A of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in water at ambient temperature of about 20-30 °C for at least 0.5 hours, to obtain a paracrystalline compound. In another embodiment, paracrystalline form B' is prepared by stirring a suspension of crystalline form A at 50 °C in water for 24h. In another embodiment paracrystalline form B' is prepared by stirring a suspension of crystalline form A at 37°C overnight to obtain paracrystalline form B'.

[00079] In one embodiment solid form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide is prepared by storage of solid form A at 40 °C

and 75% relative humidity (r.h.) for 1-2 h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 2-4h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 4-10h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 10-15h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 15-24h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 24h. In another embodiment, solid form A is stored at 40 °C and 75% r.h. for 30 days.

[00080] In one embodiment solid form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide is prepared by storage of solid form A at 40 °C and 75% relative humidity (r.h.). In another embodiment, solid form A is stored at a temperature range of about of 30-40 °C and relative humidity range of about 50-75%. In another embodiment, solid form A is stored at a temperature range of about of 40-50 °C and a relative humidity of about 60-80%. In another embodiment, solid form A is stored at a temperature range of about 40-50 °C and a relative humidity of about 60-80%.

[00081] In one embodiment, form B' is assigned as a lyotropic liquid crystalline form due to its solvent mediated formation.

[00082] In one embodiment liquid crystalline form B'' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide is prepared by melting or heating solid form A of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide to 80 °C followed by cooling.

[00083] In one embodiment form B'' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide is prepared by melting or heating to 130 °C solid form D of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide followed by cooling.

[00084] In one embodiment, evaporation of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide from solvents such as ethanol without an antisolvent yield form B''.

[00085] In one embodiment, form B'' is assigned as a thermotropic liquid crystalline form from its thermal method of preparation.

[00086] In one embodiment this invention provides a process for the preparation of solid form C of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising dissolving crystalline form A of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide in THF, followed by evaporation to obtain solid form C.

[00087] In another embodiment, form C is obtained as a mixture with form A.

[00088] In one embodiment this invention provides a process for the preparation of toluene solvate solid form of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide comprising using any solvent/antisolvent crystallization method that uses toluene as the antisolvent.

[00089] In another embodiment, the toluene solvate solid form has a melting point about 100°C with the enthalpy of melting 70±5 J/g.

[00090] In another embodiment, thermogravimetric analysis (TGA) graph of the toluene solvate in Figure 20 shows that the toluene content in the solvate is about 7% which corresponds to one toluene molecule for every three molecules of S-1. In another embodiment the toluene molecules reside inside the unit cell structure rather than in channels or layers outside the lattice. In another embodiment, the toluene solvate solid form is the most stable form in toluene.

[00091] In some embodiments, crystalline forms of the SARMs of this invention comprise alteration of a given crystalline form to one structurally similar, yet not identical to the original form. In one embodiment, such changes in crystalline forms may produce one that is more structurally stable than the original form. In some embodiments, the crystalline forms of this invention comprise altered crystalline forms, as well as original forms, in a single preparation. In some embodiments, such altered crystalline forms may comprise a small percentage of the whole SARM compound preparation, for example, up to 1%, or in another embodiment, up to 5%, or up to 10%, or up to 15%, or up to 25% of the preparation. In another embodiment, such altered forms may comprise the majority of the SARM compound preparation and may comprise 55%, or in another embodiment, 65%, or in another embodiment, 75%, or 80%, or 85%, or 90%, or 95% or up to 100% of the SARM compound preparation. In one embodiment, the favorable crystalline form is thermodynamically favorable. In another embodiment the crystalline favorable form is a result of a change in humidity. In another embodiment the crystalline favorable form is a result of a change in temperature. In another embodiment the crystalline favorable form is a result of a change in solvents.

[00092] In some embodiments, the process for the preparation of polymorph of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compounds yield various crystalline forms. In one embodiment the process yields a mixture of crystalline/paracrystalline forms A, B', C and D. In one embodiment the process yields a mixture of crystalline/paracrystalline forms A, B', B", C and D. In another embodiment, the process yields a mixture of crystalline forms A and C. In another embodiment, the process yields a mixture of crystalline/paracrystalline forms A and B'. In another embodiment, the process yields a mixture of crystalline forms A and D. In another embodiment, the process yields a mixture of crystalline/paracrystalline forms B' and D. In another embodiment, the process yields a mixture of

crystalline/paracrystalline forms B'' and D. In another embodiment, the process yields a mixture of crystalline forms C and D. In another embodiment, the process yields a mixture of crystalline/paracrystalline forms B' and C. In another embodiment, the process yields a mixture of crystalline/paracrystalline forms A and B". In another embodiment, the process yields a mixture of paracrystalline forms B' and B". In another embodiment, the process yields a mixture of crystalline/paracrystalline forms C and B". In another embodiment, the process yields a mixture of crystalline/paracrystalline forms A, C and B". In another embodiment, the process yields a mixture of crystalline/paracrystalline forms A, D and B". In another embodiment, the process yields a mixture of crystalline/paracrystalline forms B', B" and C. In another embodiment, the process yields a mixture of crystalline/paracrystalline forms A, B' and B". In another embodiment, the process yields a mixture of crystalline/paracrystalline forms D, B' and B".

[00093] In one embodiment, the solid form compounds of this invention are dried from solution by vaccuum at room temperature, followed by gradually increasing the temperature. In another embodiment, the solid form compounds of this invention are filtered from solution

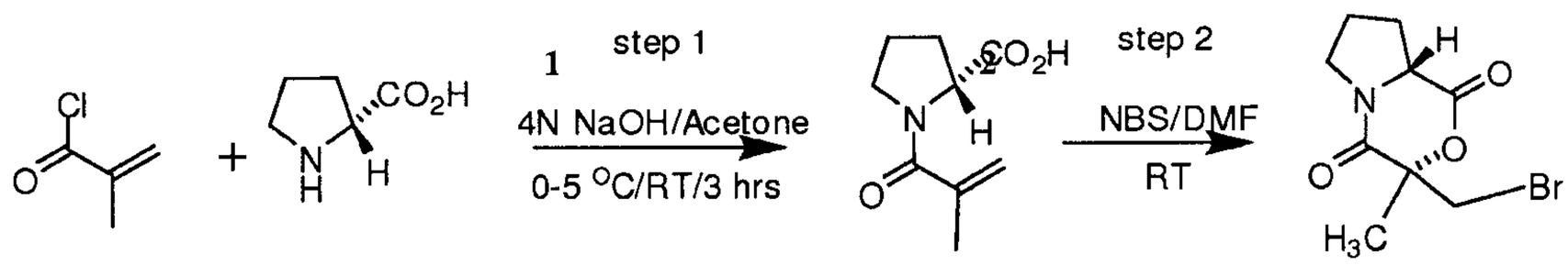
[00094] In one embodiment, the term "ambient temperature" refers to room temperature. In another embodiment, the term "ambient temperature" refers to 20-25 °C. In another embodiment, "ambient temperature" refers to 25-30 °C.

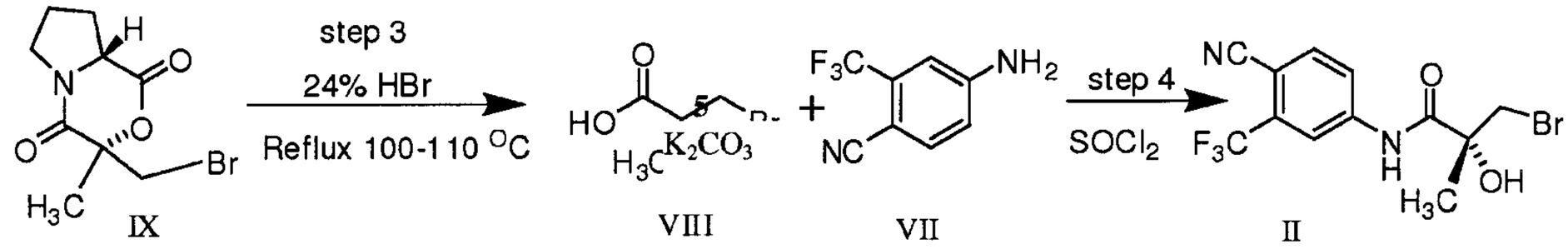
[00095] In another embodiment, form D is the most thermodynamically stable polymorph in both dry conditions and in the presence of water at ambient temperature up to its melting point of 130°C. In another embodiment, Figure 19 depicts a differential scanning calorimeter (DSC) thermogram of form A and form D, where form A melts at about 80 °C and form D melts at about 130 °C. In another embodiment, the enthalpy of melting for form A is 40 ± 5 J/g while the enthalpy of melting for form D is 75±5 J/g.

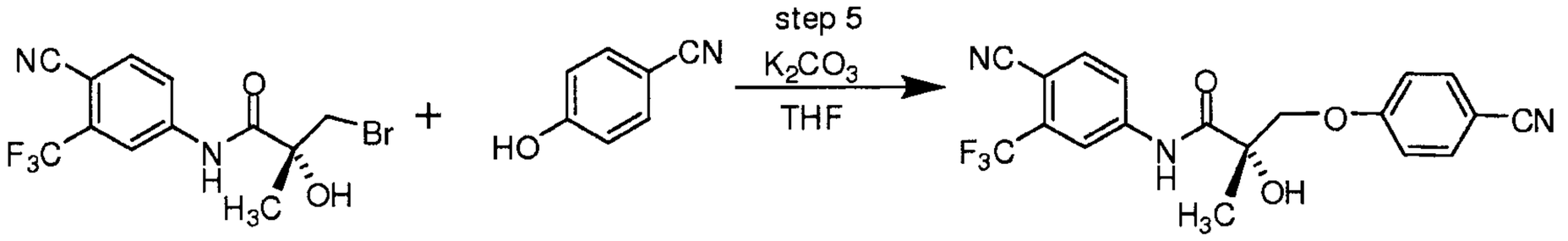
[00096] In another embodiment form A is stable in its A form for at least 7 days under storage conditions of ambient temperature/75%RH (Relative Humidity), ambient temperature/100%RH, 30°C/75%RH and 50°C/0%RH. In another embodiment, form A converts to B' when stored at 50°C/75%RH. In another embodiment, form A converts to B' when stored at 40°C/75%RH within one month. In another embodiment form A stored at 25°C/60%RH and 30°C/65%RH is stable through 36 months and 9 months respectively.

[00097] In one embodiment, (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide are prepared by chiral synthesis.

[00098] In one embodiment, the (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide may be prepared by a process according to the following synthetic scheme:



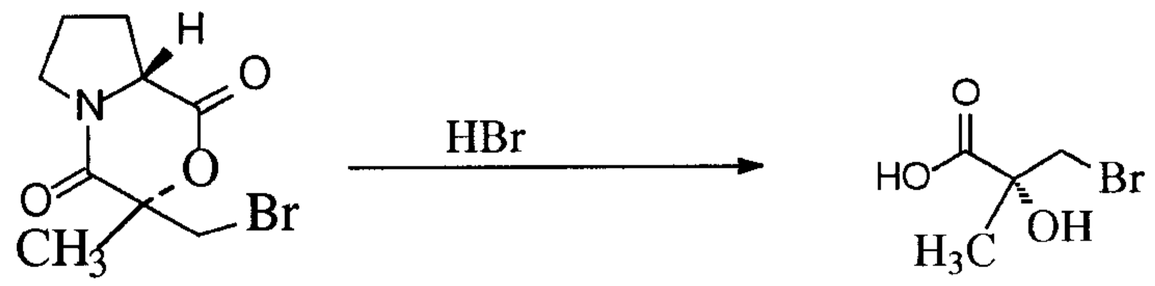




[00099] In one embodiment, the process described in the above scheme comprises reacting the acylanilide in step 5 with the cyanophenol, and such reaction may be conducted in the presence of potassium carbonate, sodium carbonate, or cesium carbonate. In one embodiment, reaction in the presence of potassium carbonate unexpectedly results in a product with fewer impurities as compared to a reaction conducted in the presence of cesium carbonate. This represents an improved and more efficient synthetic process for producing an end product, minimizing the need for additional purification steps. This finding is also advantageous to the production of other compounds such as 6, 9, 12, and 14 below.

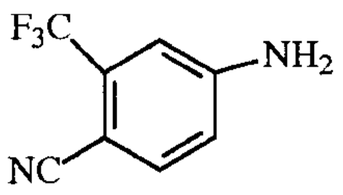
[000100] In one embodiment, this invention provides a process for preparing (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide, said process comprising the steps of:

a) preparing a carboxylic acid of formula 1 by ring opening of a cyclic compound of formula 2 in the presence of HBr



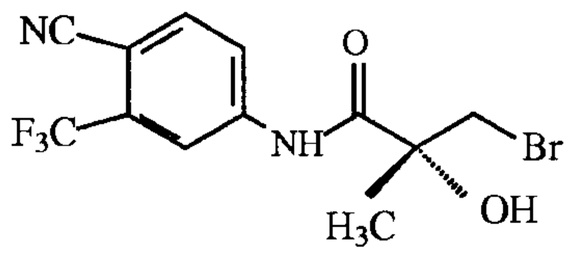
1 2

b) reacting an amine of formula 3:



3

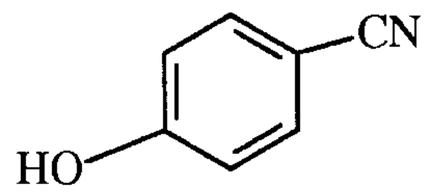
with the carboxylic acid of formula 2 in the presence of a coupling reagent, to produce an amide of formula 4



; and

4

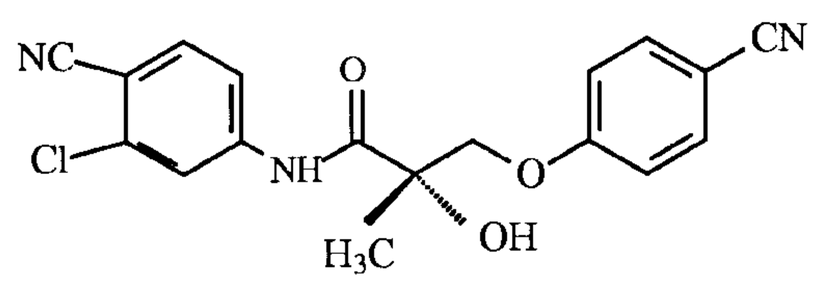
c) reacting the amide of formula 4 with a compound of formula 5:



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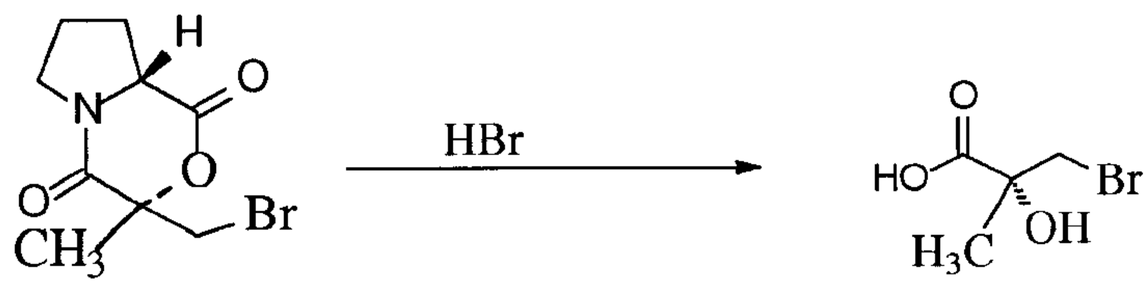
wherein step (c) is carried out in the presence of potassium carbonate and tetrahydrofuran.

[000101] In one embodiment, this invention provides a process for preparing a compound of formula 6:



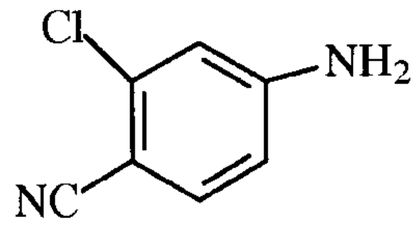
said process comprising the steps of:

a) preparing a carboxylic acid of formula 1 by ring opening of a cyclic compound of formula 2 in the presence of HBr



1 2

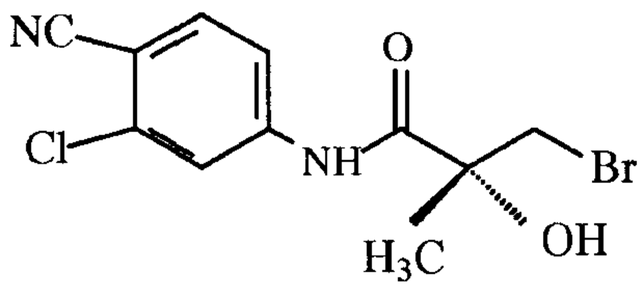
b) reacting an amine of formula 7:



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with the carboxylic acid of formula 2 in the presence of a coupling reagent, to produce an

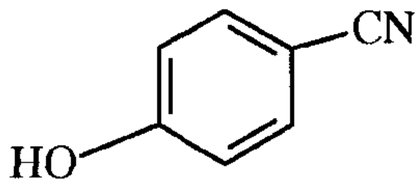
amide of formula 8:



; and

8

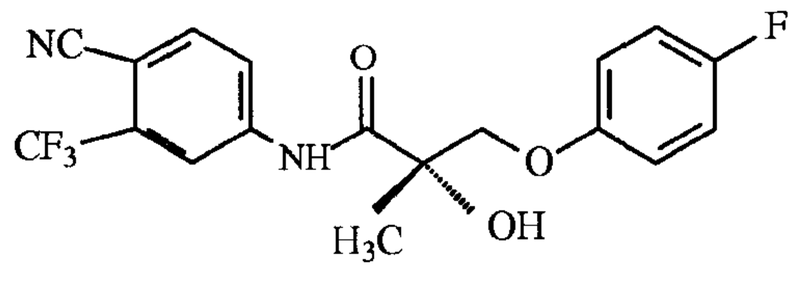
c) reacting the amide of formula 8 with a compound of formula 5:



5

wherein step (c) is carried out in the presence of potassium carbonate and tetrahydrofuran.

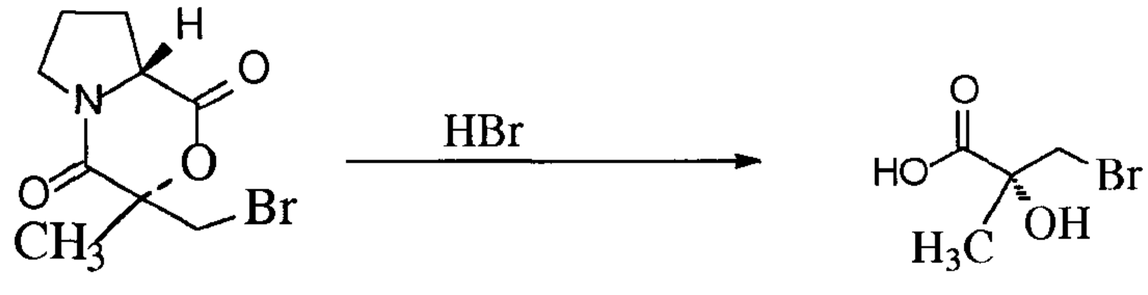
[000102] In one embodiment, this invention provides a process for preparing a compound of formula 9:



9

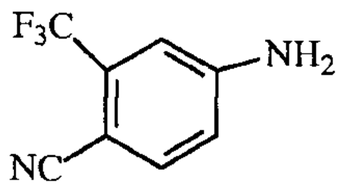
said process comprising the steps of:

a) preparing a carboxylic acid of formula 1 by ring opening of a cyclic compound of formula 2 in the presence of HBr



1 2

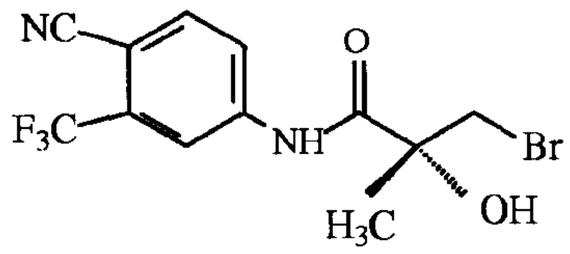
b) reacting an amine of formula 3:



3

with the carboxylic acid of formula 2 in the presence of a coupling reagent, to produce an

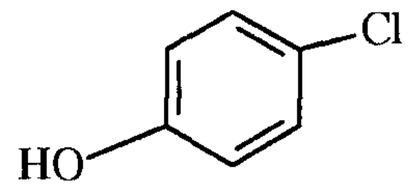
amide of formula 4



; and

4

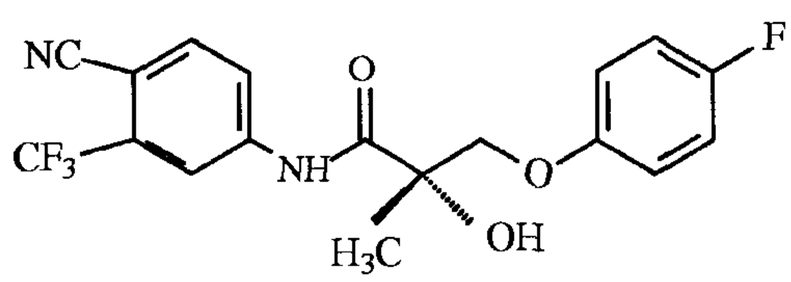
c) reacting the amide of formula 4 with a compound of formula 10:



10

wherein step (c) is carried out in the presence of potassium carbonate and tetrahydrofuran.

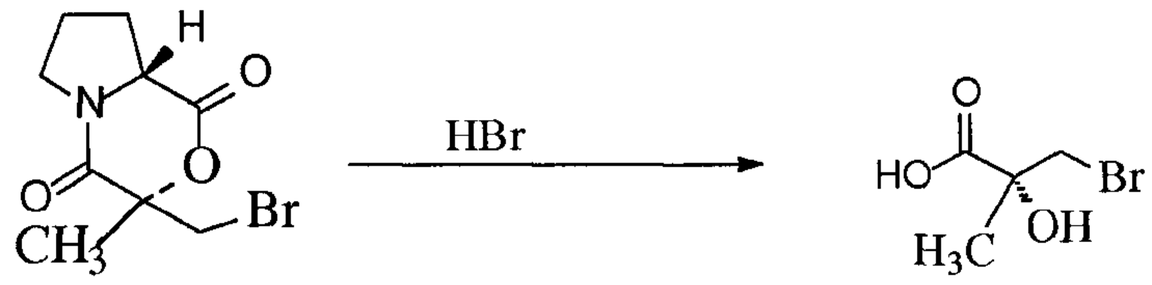
[000103] In one embodiment, this invention provides a process for preparing a compound of formula 12:



12

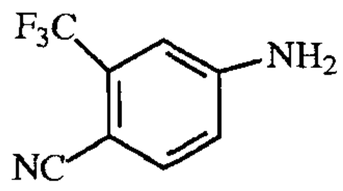
said process comprising the steps of:

a) preparing a carboxylic acid of formula 1 by ring opening of a cyclic compound of formula 2 in the presence of HBr



1 2

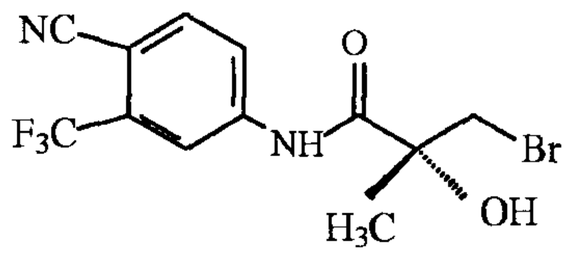
b) reacting an amine of formula 3:



3

20

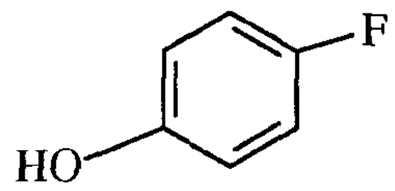
with the carboxylic acid of formula 2 in the presence of a coupling reagent, to produce an amide of formula 4



; and

4

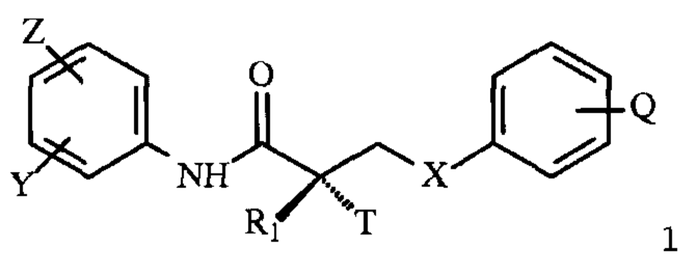
c) reacting the amide of formula 4 with a compound of formula 13:



13

wherein step (c) is carried out in the presence of potassium carbonate and tetrahydrofuran.

[000104] In one embodiment, this invention provides a process for preparing a compound of formula 14:



14

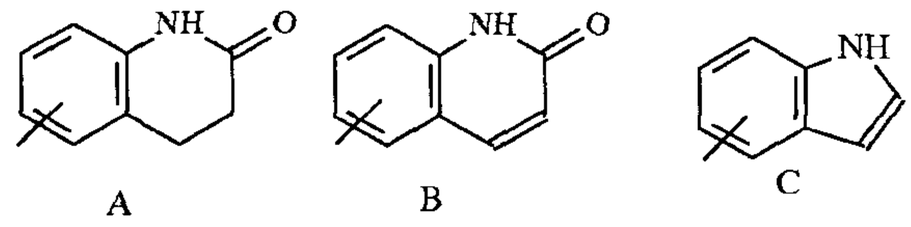
X is O, NH, Se, PR, or NR;

T is OH, OR, $NHCOCH_3$, or NHCOR;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is alkyl, halogen, CF_3, CN, CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



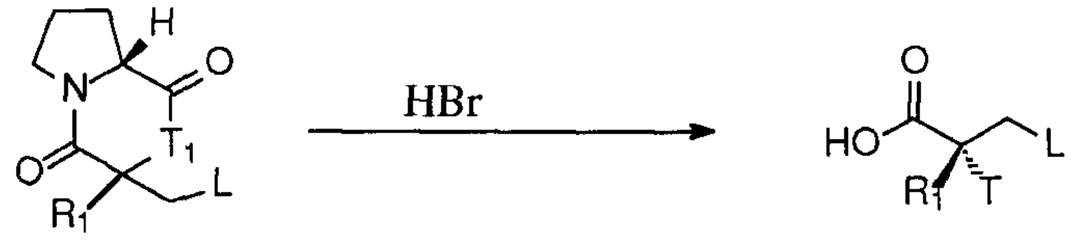
A B C

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

said process comprising the steps of:

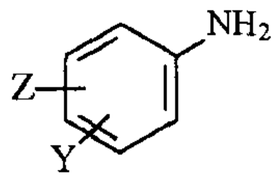
a) preparing a carboxylic acid of formula 15 by ring opening of a cyclic compound of formula 16 in the presence of HBr



16 IX 15 VIII

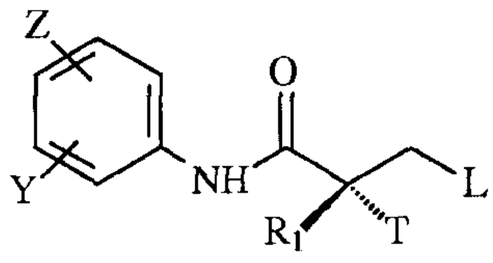
wherein L, R_1 and T are as defined above, and T_1 is O or NH;

b) reacting an amine of formula 17:



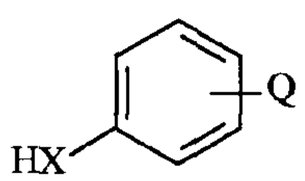
17 VII

wherein Z and Y are as defined above, with the carboxylic acid of formula 17 in the presence of a coupling reagent, to produce an amide of formula 18



18 II ; and

c) coupling the amide of formula II with a compound of formula 19:



19 III

wherein Q and X are as defined above and wherein step (c) is carried out in the presence of potassium carbonate and tetrahydrofuran.

[000105] In one embodiment, crystalline and paracrystalline forms of this invention are prepared by any process which may yield the same, such as, but not limited to those exemplified herein, as will be appreciated by one skilled in the art. In one embodiment, such a process will utilize a starting material for the preparation of crystalline and paracrystalline forms of this invention, which in turn, in some embodiments is prepared according to the method schematically depicted hereinabove. In some embodiments, preparing the starting material comprises specific reaction of the amide of formula 4 with a compound of formula 5 in the presence of potassium carbonate and

a polar solvent, such as for example and in some embodiments, tetrahydrofuran, results in the production of a highly pure preparation, which in turn may enhance the rate of crystallization. In some embodiments, use of the pure preparation as described herein, depending upon crystallization conditions employed may result in varied ratio of crystalline forms obtained. In some embodiments, use use of the pure preparation as described herein, depending upon crystallization conditions employed may result in varied ratio of crystalline forms, and the rate at which such forms are produced.

[000106] In one embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide to its analog, isomer, polymorph, polymorph form A, paracrystalline form B', solvate, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, *N*-oxide, hydrate, hemi-hydrate or any combination thereof.

[000107] In one embodiment, this invention provides a process for preparing an analog of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing an isomer of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a metabolite of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a derivative of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a pharmaceutically acceptable salt of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a pharmaceutical product of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing an *N*-oxide of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a hydrate of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a polymorph of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a polymorph form A as herein described of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a paracrystalline form B' as herein described of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a polymorph form C as herein described of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a polymorph form D as herein described of a selective androgen modulator compound of this

invention. In another embodiment, this invention provides a process for preparing a paracrystalline form of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a solvate of a selective androgen modulator compound of this invention. In another embodiment, this invention provides a process for preparing a combination of any of an analog, isomer, metabolite, derivative, polymorph, polymorph form A, paracrystalline form B', paracrystalline, solvate, pharmaceutically acceptable salt, *N*-oxide and/or hydrates of a selective androgen modulator compound of this invention. In one embodiment this invention comprises any compound thus prepared.

[000108] In one embodiment, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like.

[000109] In one embodiment, the SARMs are the pure (*R*)-enantiomer. In another embodiment, the SARMs are the pure (*S*) enantiomer. In another embodiment, the SARMs are a mixture of the (*R*) and the (*S*) enantiomers. In another embodiment, the SARMs are a racemic mixture comprising an equal amount of the (*R*) and the (*S*) enantiomers. In one embodiment, the process of the present invention further provides a step of converting the SARM compound into its optically active isomer.

[000110] In one embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises crystallization techniques. In another embodiment, the crystallization techniques include differential crystallization of enantiomers. In another embodiment, the crystallization techniques include differential crystallization of diastereomeric salts (tartaric salts or quinine salts). In another embodiment, the crystallization techniques include differential crystallization of chiral auxillary derivatives (menthol esters, etc). In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises reacting the racemate mixture with another chiral group, forming of a diastereomeric mixture followed by separation of the diastereomers and removing the additional chiral group to obtain pure enantiomers. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises chiral synthesis. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises biological resolution. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises enzymatic resolution. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises chromatographic separation using a chiral stationary phase. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer,

from the racemic SARM compounds of this invention comprises affinity chromatography. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises capillary electrophoresis. In another embodiment, separation of the optically-active (*R*) enantiomer or (*S*) enantiomer, from the racemic SARM compounds of this invention comprises forming an ester group of the hydroxyl group of the chiral carbon with an optically-active acid, for example (-)-camphanic acid, separating the diastereomers esters, thus obtained, by fractional crystallization or preferably, by flash-chromatography, and then hydrolyzing each separate ester to the alcohol.

[000111] In another embodiment the *S*-enantiomer of SARM compound of this invention can be converted to the *R*-enantiomer or to its racemate. In another embodiment the *R*-enantiomer of SARM compound of this invention can be converted to the *S*-enantiomer or to its racemate. In one embodiment, one enantiomer can be converted to the other enantiomer or its racemate by using a chiral reactant, a solvent, a biocatalyst, chiral catalyst, asymmetric hydrogenation, an enzyme, or combination thereof.

[000112] In some embodiments the solid compounds of this invention comprise solvates. In one embodiment the term "solvate" refers to solvents combined with SARM compounds, for example, a solvate of ethylacetate, which is part of a polymorph structure of the SARM compound. Such solvents include ethanol, acetone, ethylacetate, THF, acetonitrile, dichloromethane, 1,4-dioxane, acetic acid, toluene, water, *n*-heptane, toluene, *n*-pentane TBME , or any combination thereof.

[000113] In another embodiment, the process of the present invention further provides a step of converting the SARM compound into its pharmaceutically acceptable salt. In one embodiment, pharmaceutically acceptable salts include salts of amino-substituted compounds with organic and inorganic acids, for example, citric acid and hydrochloric acid. The invention also includes *N*-oxides of the amino substituents of the compounds described herein. Pharmaceutically acceptable salts can also be prepared from phenolic compounds by treatment with inorganic bases, for example, sodium hydroxide. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[000114] The invention includes “pharmaceutically acceptable salts” of the compounds of this invention, which may be produced, by reaction of a compound of this invention with an acid or base.

[000115] Suitable pharmaceutically-acceptable salts of amines of Formula I may be prepared from an inorganic acid or from an organic acid. In one embodiment, examples of inorganic salts of amines are bisulfates, borates, bromides, chlorides, hemisulfates, hydrobromates, hydrochlorates, 2-hydroxyethylsulfonates (hydroxyethanesulfonates), iodates, iodides, isothionates, nitrate, persulfates, phosphate, sulfates, sulfamates, sulfanilates, sulfonic acids (alkylsulfonates,

arylsulfonates, halogen substituted alkylsulfonates, halogen substituted arylsulfonates), sulfonates and thiocyanates.

[000116] In one embodiment, examples of organic salts of amines comprise aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are acetates, arginines, aspartates, ascorbates, adipates, anthranilate, algenate, alkane carboxylates, substituted alkane carboxylates, alginates, benzenesulfonates, benzoates, bisulfates, butyrates, bicarbonates, bitartrates, carboxilates, citrates, camphorates, camphorsulfonates, cyclohexylsulfamates, cyclopentanepropionates, calcium edetates, camsylates, carbonates, clavulanates, cinnamates, dicarboxylates, digluconates, dodecylsulfonates, dihydrochlorides, decanoates, enanthuates, ethanesulfonates, edetates, edisylates, estolates, esylates, fumarates, formates, fluorides, galacturonates, gluconates, glutamates, glycolates, glucorate, glucoheptanoates, glycerophosphates, gluceptates, glycollylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxlic acids, hexylresorcinates, hydroxybenzoates, hydroxynaphthoate, hydrofluorate, lactates, lactobionates, laurates, malates, maleates, methylenebis(beta-oxynaphthoate), malonates, mandelates, mesylates, methane sulfonates, methylbromides, methylnitrates, methylsulfonates, monopotassium maleates, mucates, monocarboxylates, mitrates, naphthalenesulfonates, 2-naphthalenesulfonates, nicotinates, napsylates, *N*-methylglucamines, oxalates, octanoates, oleates, pamoates, phenylacetates, picrates, phenylbenzoates, pivalates, propionates, phthalates, phenylacetate, pectinates, phenylpropionates, palmitates, pantothenates, polygalacturates, pyruvates, quinates, salicylates, succinates, stearates, sulfanilate, subacetates, tartarates, theophyllineacetates, *p*-toluenesulfonates (tosylates), trifluoroacetates, terephthalates, tannates, teoclates, trihaloacetates, triethiodide, tricarboxylates, undecanoates or valerates.

[000117] In one embodiment, examples of inorganic salts of carboxylic acids or phenols comprise ammonium, alkali metals to include lithium, sodium, potassium, cesium; alkaline earth metals to include calcium, magnesium, aluminium; zinc, barium, cholines or quaternary ammoniums.

[000118] In another embodiment, examples of organic salts of carboxylic acids or phenols comprise arginine, organic amines to include aliphatic organic amines, alicyclic organic amines, aromatic organic amines, benzathines, *t*-butylamines, benethamines (*N*-benzylphenethylamine), dicyclohexylamines, dimethylamines, diethanolamines, ethanolamines, ethylenediamines, hydrabamines, imidazoles, lysines, methylamines, meglamines, *N*-methyl-D-glucamines, *N,N'*-dibenzylethylenediamines, nicotinamides, organic amines, ornithines, pyridines, picolinates, piperazines, procain, tris(hydroxymethyl)methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines or ureas.

[000119] In one embodiment, the salts may be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the ions of a existing salt for another ion or suitable ion-exchange resin.

[000120] In one embodiment, the invention also includes *N*-oxides of the amino substituents of the compounds described herein. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[000121] This invention further includes a process for preparing derivatives of the SARM compounds. In some embodiments, the term "derivative" includes, but is not limited to, ether derivatives, acid derivatives, amide derivatives, ester derivatives and the like. Methods of preparing derivatives are known to a person skilled in the art. For example, ether derivatives are prepared by coupling of the corresponding alcohols. Amide and ester derivatives are prepared from the corresponding carboxylic acid by a reaction with amines and alcohols, respectively.

[000122] In some embodiments, this invention comprises a process for preparing hydrates of the SARM compounds. In one embodiment the term "hydrate" includes, but is not limited to, hemi-hydrate, monohydrate, dihydrate, trihydrate and the like. Hydrates of the SARM compounds may be prepared by contacting the SARM compound with water under suitable conditions to produce the hydrate of choice. The term "hemi-hydrate" refers to hydrate in which the molecular ratio of water molecules to anhydrous compound is 1:2.

[000123] This invention further includes a process for preparing pharmaceutical products of the SARM compounds. The term "pharmaceutical product" means a composition suitable for pharmaceutical use (pharmaceutical composition), as defined herein.

[000124] In some embodiments, this invention comprises a process for preparing analogs of the SARM compounds. In one embodiment the term "analog" refers to a compound with a structure, which is similar, but not identical to that of the referenced compound. In another embodiment the term "analog" refers to an isomer or derivative of the SARM compound. In another embodiment the term "analog of a SARM compound" of this invention refers to a compound having different substituents on each or both phenyl rings in the compound. In another embodiment, the term "analog" refers to the incorporation of different aromatic rings, for example pyridyl rings, in place of the one or both benzene rings. In another embodiment, the term "analog" refers to the incorporation of a sulfur atom instead of each or both ether and keto groups.

[000125] In some embodiments, this invention comprises a metabolite of the SARM compounds. The term "metabolite" refers, in some embodiments to any substance produced from another substance by mimicking or via metabolic process. In some embodiment such metabolites can be

prepared synthetically and are active *in situ*, as they are comparable to naturally produced metabolites.

Pharmaceutical Compositions

[000126] In one embodiment, this invention provides a composition comprising a crystalline form of anhydrous (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[000127] In another embodiment, this invention provides a composition comprising a crystalline form A of anhydrous (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[000128] In one embodiment, this invention provides a composition comprising a paracrystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[000129] In one embodiment, this invention provides a composition comprising a paracrystalline form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide and a suitable carrier or diluent.

[000130] In one embodiment, this invention provides a composition comprising a mixture of any solid forms of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound of this invention and a suitable carrier or diluent.

[000131] In another embodiment, this invention provides a composition comprising a mixture of crystalline and paracrystalline solid forms of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound and a suitable carrier or diluent.

[000132] In another embodiment, this invention provides a composition comprising a mixture of crystalline form A and paracrystalline solid form B' of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound and a suitable carrier or diluent.

[000133] In one embodiment, this invention encompasses compositions comprising the different forms of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide they can be in different ratios or a single form per composition, which possesses properties useful in the treatment of androgen-related conditions described herein. In another embodiment, this invention encompasses compositions comprising different isomers of *N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide, they can be in different ratios or a single isomer per composition, which possesses properties useful in the treatment of androgen-related conditions described herein.

[000134] In some embodiments, the phrase, "pharmaceutical composition" refers to a "therapeutically effective amount" of the active ingredient, i.e. the SARM compound, together

with a pharmaceutically acceptable carrier or diluent. In some embodiments, the phrase "therapeutically effective amount" refers to an amount which provides a therapeutic effect for a given condition and administration regimen.

[000135] The pharmaceutical compositions containing the SARM agent can be administered to a subject by any method known to a person skilled in the art, such as parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitoneally, intraventricularly, intracranially or intratumorally.

[000136] In another embodiment this invention provides, a composition of the solid forms of this invention and a suitable carrier or diluent.

[000137] In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e. as a solid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets and the like. In one embodiment of the present invention, the SARM compounds are formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the SARM active compound and the inert carrier or diluent, a hard gelating capsule.

[000138] Oral formulations containing the present polymorph can comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, or lozenges. Capsules may contain mixtures of the crystalline form A in the desired percentage together any other polymorph(s) of SARM or amorphous SARM. Capsules or tablets of the desired crystalline form of the desired percentage composition may also be combined with mixtures of other active compounds or inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc.

[000139] Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents (fillers), binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations, in some embodiments, utilize standard delay or time release formulations or spansules.

[000140] Example excipient systems suitable for preparing formulations of the present polymorph include one or more fillers, disintegrants, and lubricants.

[000141] The filler component can be any filler component known in the art including, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

[000142] Disintegrants suitable for use in the present formulations can be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium carbonate, etc.). The disintegrant(s) useful herein can comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%.

[000143] The pharmaceutical formulations can also contain an antioxidant or a mixture of antioxidants, such as ascorbic acid. Other antioxidants which can be used include sodium ascorbate and ascorbyl palmitate, preferably in conjunction with an amount of ascorbic acid. An example range for the antioxidant(s) is from about 0.5% to about 15% by weight, most preferably from about 0.5% to about 5% by weight.

[000144] In some embodiments of this invention, the active pharmacological agent(s) comprise from about 0.5% to about 20%, by weight, of the final composition, or in some embodiments, from about 1% to about 5%, and the coating or capsule comprises up to about 8%, by weight, of the final composition.

[000145] The formulations described herein can be used in an uncoated or non-encapsulated solid form. In some embodiments, the pharmacological compositions are optionally coated with a film coating, for example, comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

[000146] In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

[000147] As used herein "pharmaceutically acceptable carriers or diluents" are well known to those skilled in the art. The carrier or diluent may be a solid carrier or diluent for solid formulations.

[000148] Solid carriers/diluents include, but are not limited to, a gum, a starch (e.g. corn starch, pregeletanized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g. microcrystalline cellulose), an acrylate (e.g. polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

[000149] In addition, the compositions may further comprise binders (e.g. acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g. cornstarch, potato starch, alginic acid, silicon dioxide, croscarmelose sodium, crospovidone, guar gum, sodium starch glycolate), buffers (e.g., Tris-HCI, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g. sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g. hydroxypropyl cellulose, hyroxypropylmethyl cellulose), viscosity increasing agents (e.g. carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweetners (e.g. aspartame, citric acid), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g. stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g. colloidal silicon dioxide), plasticizers (e.g. diethyl phthalate, triethyl citrate), emulsifiers (e.g. carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g. ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

[000150] In one embodiment, the pharmaceutical compositions provided herein are controlled release compositions, i.e. compositions in which the SARM compound is released over a period of time after administration. In another embodiment, the composition is an immediate release composition, i.e. a composition in which all of the SARM compound is released immediately after administration.

[000151] In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. For example, the agent may be administered using liposomes, or other modes of oral administration.

[000152] The compositions may also include incorporation of the active material into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance.

[000153] The preparation of pharmaceutical compositions which contain an active component is well understood in the art, for example by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the SARM agents or their physiologically tolerated derivatives such as salts, esters, *N*-oxides, and the like are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions.

[000154] An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide or antibody molecule), which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[000155] For use in medicine, the salts of the SARM will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic: acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Biological Activity of Selective Androgen Modulator Compounds

[000156] The solid forms and processes for producing the same provided herein are, in some embodiments, directed to selective androgen receptor modulators (SARMs), which are useful for oral testosterone replacement therapy, having unexpected *in-vivo* androgenic and anabolic activity. In some embodiments, appropriately substituted compounds are effective to treat prostate cancer and useful for imaging of prostate cancer.

[000157] As contemplated herein, the appropriately substituted SARM compounds of the present invention are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis,

benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of chronic muscular wasting; e) decreasing the incidence of, halting or causing a regression of prostate cancer; f) oral androgen relacement and/or other clinical therapeutic and/or diagnostic areas.

[000158] As used herein, receptors for extracellular signaling molecules are collectively referred to as "cell signaling receptors". Many cell signaling receptors are transmembrane proteins on a cell surface; when they bind an extracellular signaling molecule (i.e., a ligand), they become activated so as to generate a cascade of intracellular signals that alter the behavior of the cell. In contrast, in some cases, the receptors are inside the cell and the signaling ligand has to enter the cell to activate them; these signaling molecules therefore must be sufficiently small and hydrophobic to diffuse across the plasma membrane of the cell. As used herein, these receptors are collectively referred to as "intracellular cell signaling receptors".

[000159] Steroid hormones are one example of small hydrophobic molecules that diffuse directly across the plasma membrane of target cells and bind to intracellular cell signaling receptors. These receptors are structurally related and constitute the intracellular receptor superfamily (or steroid-hormone receptor superfamily). Steroid hormone receptors include progesterone receptors, estrogen receptors, androgen receptors, glucocorticoid receptors, and mineralocorticoid receptors. The present invention is particularly directed to androgen receptors.

[000160] In addition to ligand binding to the receptors, the receptors can be blocked to prevent ligand binding. When a substance binds to a receptor, the three-dimensional structure of the substance fits into a space created by the three- dimensional structure of the receptor in a ball and socket configuration.

[000161] In one embodiment, the present invention is directed to processes for preparing solid forms of selective androgen receptor modulator compounds which are agonist compounds. Thus, in one embodiment, the SARM compounds of the present invention are useful in binding to and activating steroidal hormone receptors. In one embodiment, the agonist compound of the present invention is an agonist which binds the androgen receptor. In another embodiment, the compound has high affinity for the androgen receptor. In another embodiment, the agonist compound also has anabolic activity. In another embodiment, the present invention provides selective androgen modulator compounds which have agonistic and anabolic activity of a nonsteroidal compound for the androgen receptor.

[000162] In one embodiment, the present invention is directed to processes for preparing solid forms of selective androgen receptor modulator compounds which are antagonist compounds. Thus, in one embodiment, the solid forms of the SARM compounds of the present invention are useful in binding to and inactivating steroidal hormone receptors. In another embodiment, the the solid forms of the invention have a high affinity for the androgen receptor. In another embodiment, the the solid forms of this invention also have anabolic activity. In another embodiment, the the solid forms of the SARM compounds bind irreversibly to the androgen receptor. In another embodiment, the solid forms of the SARM compounds are alkylating agents.

[000163] In yet another embodiment, the solid forms of the SARM compounds of the present invention can be classified as partial AR agonist/antagonists. The the solid forms of the SARMs are AR agonists in some tissues, and cause increased transcription of AR-responsive genes (e.g. muscle anabolic effect). In other tissues, these compounds serve as inhibitors at the AR to prevent agonistic effects of the native androgens.

[000164] Assays to determine whether the compounds of the present invention are AR agonists or antagonists are well known to a person skilled in the art. For example, AR agonistic activity can be determined by monitoring the ability of the solid forms of the SARM compounds to maintain and/or stimulate the growth of AR containing tissue such as prostate and seminal vesicles, as measured by weight. AR antagonistic activity can be determined by monitoring the ability of the SARM compounds to inhibit the growth of AR containing tissue.

[000165] In another embodiment, the solid forms of the SARM compounds bind irreversibly to the androgen receptor of a mammal, for example a human. Thus, in one embodiment, the compounds of the present invention may contain a functional group (e.g. affinity label) that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in this case, the compounds are alkylating agents which bind irreversibly to the receptor and, accordingly, cannot be displaced by a steroid, such as the endogenous ligands DHT and testosterone. An "alkylating agent" is defined herein as an agent which alkylates (forms a covalent bond) with a cellular component, such as DNA, RNA or protein. It is a highly reactive chemical that introduces alkyl radicals into biologically active molecules and thereby prevents their proper functioning. The alkylating moiety is an electrophilic group that interacts with nucleophilic moieties in cellular components.

[000166] According to one embodiment of the present invention, a method is provided for binding the solid forms of the SARM compounds of the present invention to an androgen receptor by contacting the receptor with the solid forms of the SARM compound, such as polymorph form A, polymorph form C, polymorph form D, paracrystalline form B', paracrystalline B'', a solvate thereof, a polymorph thereof, a metabolite thereof, etc., or any combination thereof, under conditions effective to cause the selective androgen receptor modulator compound to bind the

androgen receptor. The binding of the solid forms of the selective androgen receptor modulator compounds to the androgen receptor enables the compounds of the present invention to be useful as a male contraceptive and in a number of hormone therapies. The agonist compounds bind to and activate the androgen receptor. The antagonist compounds bind to and inactivate the androgen receptor. Binding of the agonist or antagonist compounds is either reversible or irreversible.

[000167] In one embodiment, the solid forms of the SARM compounds of the present invention are administered as the sole active ingredient. However, also encompassed within the scope of the present invention are methods for hormone therapy, for treating prostate cancer, for delaying the progression of prostate cancer, and for preventing and/or treating the recurrence of prostate cancer, which comprise administering the solid forms of the SARM compounds in combination with one or more therapeutic agents. These agents include, but are not limited to: LHRH analogs, reversible antiandrogens, antiestrogens, anticancer drugs, 5-alpha reductase inhibitors, aromatase inhibitors, progestins, agents acting through other nuclear hormone receptors, selective estrogen receptor modulators (SERM), progesterone, estrogen, PDE5 inhibitors, apomorphine, bisphosphonate, and one or more solid forms of the SARMS, for example one with AR agonistic activity.

[000168] Thus, in one embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with an LHRH analog. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with a reversible antiandrogen. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with an antiestrogen. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with an anticancer drug. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with an aromatase inhibitor. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with a progestin. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with an agent acting through other

nuclear hormone receptors. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with a selective estrogen receptor modulators (SERM). In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with progesterone. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with estrogen. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with PDE5 inhibitors. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with apomorphine. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with a bisphosphonate. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising the solid forms of the selective androgen receptor modulator compound, in combination with one or more additional SARMs.

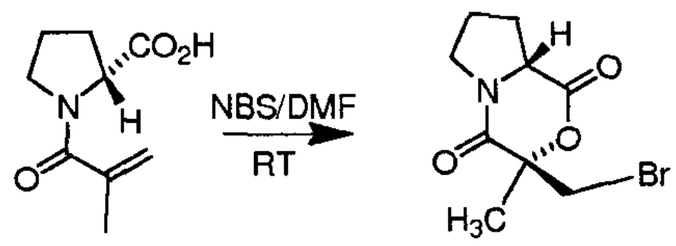
[000169] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXPERIMENTAL DETAILS SECTION

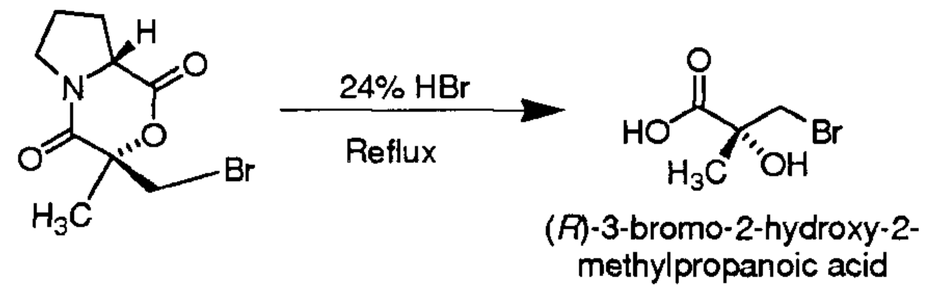
EXAMPLE 1: SYNTHESIS OF COMPOUND S-1

[000170] **(2*R*)-1-Methacryloylpyrrolidin–2-carboxylic Acid.** *D*-Proline, 14.93 g, 0.13 mol) was dissolved in 71 mL of 2 N NaOH and cooled in an ice bath; the resulting alkaline solution was diluted with acetone (71 mL). An acetone solution (71 mL) of methacrylolyl chloride (13.56 g, 0.13 mol) and 2N NaOH solution (71 mL) were simultaneously added over 40 min to the aqueous solution of *D*-proline in an ice bath. The pH of the mixture was kept at 10-11°C during the addition of the methacrylolyl chloride. After stirring (3 h, room temperature), the mixture was evaporated *in vacuo* at a temperature at 35-45 °C to remove acetone. The resulting solution was washed with ethyl ether and was acidified to pH 2 with concentrated HCl. The acidic mixture was saturated with NaCl and was extracted with EtOAc (100 mL x 3). The combined extracts were dried over Na_2SO_4, filtered through Celite™ and evaporated *in vacuo* to give the crude product as a colorless oil. Recrystallization of the oil from ethyl ether and hexanes afforded 16.2 (68%) of the

desired compound as colorless crystals: mp 102-103 °C (lit. [214] mp 102.5-103.5 °C); the NMR spectrum of this compound demonstrated the existence of two rotamers of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.28 (s) and 5.15 (s) for the first rotamer, 5.15 (s) and 5.03 (s) for the second rotamer (totally 2H for both rotamers, vinyl CH_2), 4.48-4.44 for the first rotamer, 4.24-4.20 (m) for the second rotamer (totally 1H for both rotamers, CH at the chiral canter), 3.57-3.38 (m, 2H, CH_2), 2.27-2.12 (1H, CH), 1.97-1.72 (m, 6H, CH_2, CH, Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ for major rotamer 173.3, 169.1, 140.9, 116.4, 58.3, 48.7, 28.9, 24.7, 19.5: for minor rotamer 174.0, 170.0, 141.6, 115.2, 60.3, 45.9, 31.0, 22.3, 19.7; IR (KBr) 3437 (OH), 1737 (C=O), 1647 (CO, COOH), 1584, 1508, 1459, 1369, 1348, 1178 cm^{-1}; $[\alpha]_D^{26}$ +80.8° (c = 1, MeOH); Anal. Calcd. for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65. Found: C 59.13, H 7.19, N 7.61.

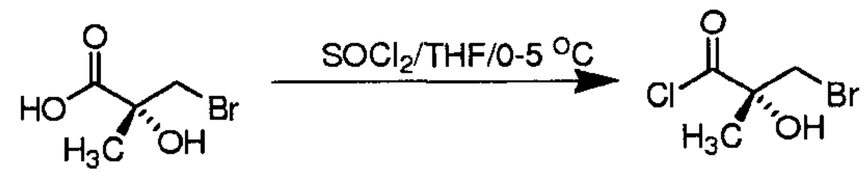


[000171] **(3*R*,8a*R*)-3-Bromomethyl-3-methyl-tetrahydro-pyrrolo[2,1-*c*][1,4]oxazine-1,4-dione.** A solution of NBS (23.5g, 0.132 mol) in 100 mL of DMF was added dropwise to a stirred solution of the (methyl-acryloyl)-pyrrolidine (16.1g, 88 mmol) in 70 mL of DMF under argon at room temperature, and the resulting mixture was stirred 3 days. The solvent was removed *in vacuo*, and a yellow solid was precipitated. The solid was suspended in water, stirred overnight at room temperature, filtered, and dried to give 18.6 (81%) (smaller weight when dried ~ 34%) of the title compound as a yellow solid: mp 152-154 °C (lit. [214] mp 107-109 °C for the *S*-isomer); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.69 (dd, J = 9.6 Hz, J = 6.7 Hz, 1H, CH at the chiral center), 4.02 (d, J = 11.4 Hz, 1H, CHH_a), 3.86 (d, J = 11.4 Hz, 1H, CHH_b), 3.53-3.24 (m, 4H, CH_2), 2.30-2.20 (m, 1H, CH), 2.04-1.72 (m, 3H, CH_2 and CH), 1.56 (s, 2H, Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3, 163.1, 83.9, 57.2, 45.4, 37.8, 29.0, 22.9, 21.6; IR (KBr) 3474, 1745 (C=O), 1687 (C=O), 1448, 1377, 1360, 1308, 1227, 1159, 1062cm^{-1}; $[\alpha]_D^{26}$ +124.5 ° (c = 1.3, chloroform); Anal. Calcd. for $C_9H_{12}BrNO_3$: C 41.24, H 4.61, N 5.34. Found: C 41.46, H 4.64, N 5.32.



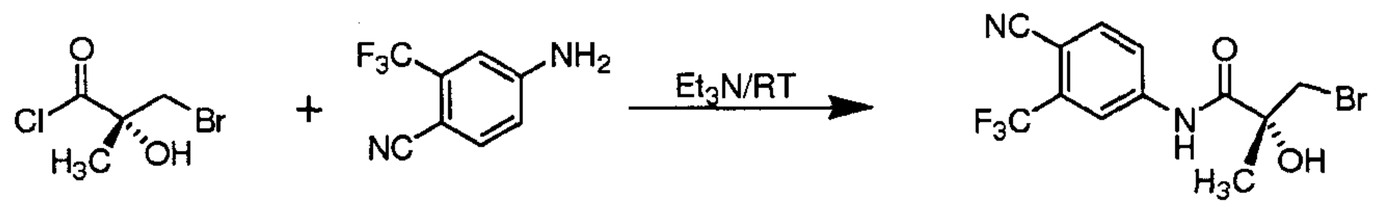
[000172] **(2*R*)-3-Bromo-2-hydroxy-2-methylpropanoic Acid.** A mixture of bromolactone (18.5g, 71 mmol) in 300 mL of 24% HBr was heated at reflux for 1 h. The resulting solution was diluted

with brine (200 mL), and was extracted with ethyl acetate (100 mL x 4). The combined extracts were washed with saturated $NaHCO_3$ (100 mL x 4). The aqueous solution was acidified with concentrated HCl to pH = 1, which, in turn, was extracted with ethyl acetate (100 mL x 4). The combined organic solution was dried over Na_2SO_4, filtered through Celite, and evaporated *in vacuo* to dryness. Recrystallization from toluene afforded 10.2 g (86%) of the desired compound as colorless crystals: mp 107-109 °C (lit. [214] mp 109-113 °C for the *S*-isomer); ^1H NMR (300 MHz, DMSO-d_6) δ 3.63 (d, J = 10.1 Hz, 1H, CHH_a), 3.52 (d, J = 10.1 Hz, 1H, CHH_b), 1.35 (s, 3H, Me); IR (KBr) 3434 (OH), 3300-2500 (COOH), 1730 (C=O), 1449, 1421, 1380, 1292, 1193, 1085 cm^{-1}; $[\alpha]_D^{26}$ +10.5° (c = 2.6, MeOH); Anal. Calcd. for $C_4H_7BrO_3$: C 26.25, H 3.86. Found: C 26.28, H 3.75.



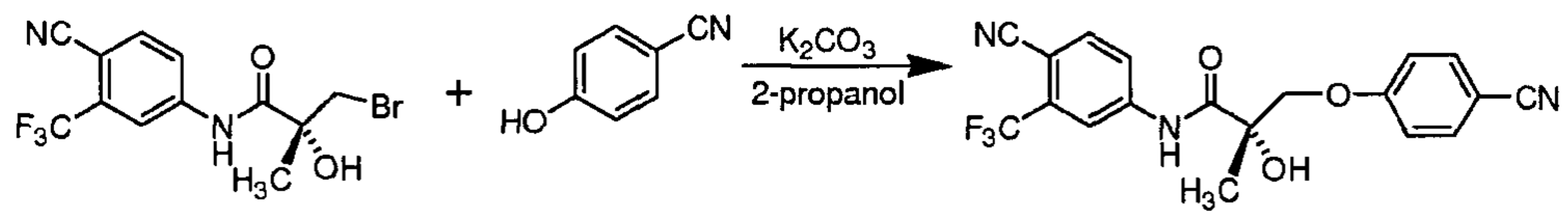
(*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid

6



[000173] **Synthesis of (2*R*)-3-Bromo-*N*-[4-cyano-3-(trifluoromethyl) phenyl]-2-hydroxy-2-methylpropanamide.** Thionyl chloride (46.02 g, 0.39 mol) was added dropwise to a cooled solution (less than 4°C) of **6** (51.13 g, 0.28 mol) in 300 mL of THF under an argon atmosphere. The resulting mixture was stirred for 3 h under the same condition. To this was added Et_3N (39.14 g, 0.39 mol) and stirred for 20 min under the same condition. After 20 min, 5-amino-2-cyanobenzotrifluoride (40.0 g, 0.21 mol), 400 mL of THF were added and then the mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure to give a solid which was treated with 300 mL of H_2O, extracted with EtOAc (2 X 400 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 X 300 mL) and brine (300 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a solid which was purified from column chromatography using CH_2Cl_2/EtOAc (80:20) to give a solid. This solid was recrystallized from CH_2Cl_2/hexane to give 55.8 g (73.9%) of (2*R*)-3-Bromo-*N*-[4-cyano-3-(trifluoromethyl) phenyl]-2-hydroxy-2-methylpropanamide as a light-yellow solid.

[000174] ^{1}H NMR ($CDCl_3$/TMS) δ 1.66 (s, 3H, C*H*$_3$), 3.11 (s, 1H, O*H*), 3.63 (d, *J* = 10.8 Hz, 1H, C*H*$_2$), 4.05 (d, *J* = 10.8 Hz, 1H, C*H*$_2$), 7.85 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.99 (dd, *J* = 2.1, 8.4 Hz, 1H, Ar*H*), 8.12 (d, *J* = 2.1 Hz, 1H, Ar*H*), 9.04 (bs, 1H, N*H*). Calculated Mass: 349.99, $[M-H]^-$ 349.0. M.p.: 124-126 °C.



(2*R*)-3-bromo-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide

(*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide

[000175] **Synthesis of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide.** A mixture of bromoamide ((2*R*)-3-bromo-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide, 50 g, 0.14 mol), anhydrous K_2CO_3 (59.04 g, 0.43 mol), and 4-cyanophenol (25.44 g, 0.21 mol) in 500 mL of 2-propanol was heated to reflux for 3 h and then concentrated under reduced pressure to give a solid. The resulting residue was treated with 500 mL of H_2O and then extracted with EtOAc (2 × 300 mL). The combined EtOAc extracts were washed with 10% NaOH (4 × 200 mL) and brine. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure to give an oil which was treated with 300 mL of ethanol and an activated carbon. The reaction mixture was heated to reflux for 1 h and then the hot mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to give an oil. This oil was purified by column chromatography using CH_2Cl_2/EtOAc (80:20) to give an oil which was crystallized from CH_2Cl_2/hexane to give 33.2 g (59.9%) of (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide as a colorless solid (a cotton type).

^{1}H NMR ($CDCl_3$/TMS) δ 1.63 (s, 3H, C*H*$_3$), 3.35 (s, 1H,O*H*), 4.07 (d, *J* = 9.04 Hz, 1H, C*H*), 4.51 (d, *J* = 9.04 Hz, 1H, C*H*), 6.97 – 6.99 (m, 2H, Ar*H*), 7.57-7.60 (m, 2H, Ar*H*), 7.81 (d, *J* = 8.55 Hz, 1H, Ar*H*), 7.97 (dd, *J* = 1.95, 8.55 Hz, 1H, Ar*H*), 8.12 (d, *J* = 1.95 Hz, 1H, Ar*H*), 9.13 (bs, 1H, N*H*). Calculated Mass: 389.10, $[M-H]^-$ 388.1. Mp: 92-94 °C.

EXAMPLE 2: CRYSTALLIZATION OF S-1 SARM COMPOUND

Materials and Methods

Methods:

X-ray powder diffraction (XRPD)

[000176] XRPD was used for the determination of the crystal structure or recognition of liquid

crystals materials in partially crystalline mixtures. XRPD was performed with PANalytical X-ray diffractometer PW 1710, where the tube anode was Cu with Ka radiation. The pattern was collected in step scan mode (step size of 0.02 °2θ , counting time 2.4 s/step. The sample was measured without any special treatment other than the application of slight pressure to get a flat surface. The measurements were performed at an ambient air atmosphere.

Raman Spectroscopy

[000177] FT-Raman spectra were recorded on a Bruker RFS 100 FT-Raman system with a near infrared Nd:YAG laser operating at 1064 nm and a liquid nitrogen-cooled germanium detector. For each sample, 64 scans with a resolution of 2 cm^{-1} were accumulated. The laser power used was at 100 mW. Raman measurements were conducted using aluminum sample holders or hermetically closed glass tubes at room temperature.

Thermo Gravimetric –FourierTransform Infrared (TG-FTIR) and Thermo Gravimetric Analysis

[000178] The TG-FTIR instrument consists of a thermogravimetric analyzer (TG) coupled with a Fourier-Transform Infrared (FTIR) spectrometer for the analysis of evolved gases such as gases of H_2O, by their mass loss combined with characterization of the evolved components. Thermo gravimetric measurements were carried out with a Netzsch Thermo-Microbalance TG 209 coupled to a Bruker FTIR Spectrometer Vector 22. Sample pans with a pinhole were used under an N_2 atmosphere, at a heating rate of 10 K/min, with a temperature range of 25 to 250°C. Additional Thermo Gravimetric Analysis was conducted using a TA Instruments Q500 TGA under various conditions.

Differential scanning calorimetry (DSC)

[000179] Thermal analysis was carried out with a Perkin Elmer DSC7 with the following experimental conditions: 3 to 6 mg sample mass, closed gold sample pan, temperature range -50°C to 120°C, heating rate 20 K/min. The samples were weighed in air or dry N_2 atmosphere. Additional thermal analysis was conducted using a TA Instruments Q1000 DSC using hermetic aluminum pans under various conditions.

Dynamic Vapor Sorption (DVS)

[000180] Dynamic vapor sorption quantification relates the mass of water absorbed and subsequently desorbed during the crystallization process. In order to define whether batch P1, P2 and P4 are hydrated polymorphs, DVS measurements were conducted (Figure 9). A sample (13 to 14 mg) was placed on a Pt pan, and the sample was allowed to equilibrate at 25°C / 50% r.h. before starting a pre-defined humidity program (1.0 hours 50%, from 50 % r.h. to 95% r.h.: 5% r.h./hour, 10 hours at 95% r.h., from 95 % r.h. to 0% r.h.: 5% r.h./hour, 10 hours at 0% r.h., from 0 % r.h. to 50% r.h.: 5% r.h./hour, 1 hours at 50% r.h.

Scanning Electron Spectroscopy(SEM)

[000181] Images of **S-1** batch P1, P2 and P4 (Figure 8) were taken with an SEM CamScan CS24 system.

Filtration

[000182] During the following experiments: suspension equilibration, precipitation experiment, recrystallization, relative stability experiments and water solubility experiment, a filtration step was conducted. Centrifugal filter devices: Ultrafree-CL (0.22 la,m), Millipore; Centrifuge type or Eppendorf 5804R were used at a temperature of22°C and centrifugation program of 2 min 3000 rpm.

High Performance Liquid Chromatography (HPLC)

[000183] HPLC was used to analyse the purity of **S-1.** HP 1090M HPLC machine was used with the following conditions:

Column: Symmetry Shield RP18, 3.9 x 150 mm, 5 µm

Column temperature: 35°C

Injection volume: 10 µL

Solvent: acetonitrile + water 1:1 v/v

Mobile phase A: 0.1% TFA - water

Mobile phase B: 0.1% TFA - acetonitrile

Flow rate: 1 mL / min.

Detection: UV at 271 nm

Run time: 21 min.

Retention time (**S-1**): 10.7 min.

Materials:

Solvents

[000184] For all experiments, Fluka or Merck grade solvents were used. Water: deionized (Fluka no. 95305)

Chemicals

[000185] Compound **S-1** was synthesized as described in Example 1.

Results:

[000186] Four batches of **S-1** compound designated accordingly, (S-1-P1), (S-1-P2), (S-1-P3), and (S-1-P4) were selected for characterization. S-1-P1, S-1-P2, and S-1-P3 were individual batches prepared by the synthetic process described in Example 1. Batch S-1-P4 was a sample of batch S-1-P1 exposed to 40 C/75% r.h. during storage. The following experiments were conducted to determine the stability, solubility and characteristics of different solid forms of **S-1** compound.

[000187] The following table presents the X-ray diffraction results of form A of **S-1** as depicted in

Figure 4A:

Angle 2-Theta °	d value Angstrom	Intensity Cps	Intensity % %
5.56	15.9	2250	30
7.47	11.8	470	6
8.61	10.3	1399	19
9.93	8.9	3016	40
12.41	7.1	707	9
14.94	5.93	2647	35
16.66	5.32	6922	92
17.31	5.12	1049	14
18.03	4.92	397	5
18.52	4.79	930	12
19.25	4.61	830	11
19.83	4.47	823	11
20.63	4.30	740	10
21.80	4.07	988	13
22.33	3.98	7557	100
23.45	3.79	976	13
23.92	3.72	914	12
24.56	3.62	376	5
24.92	3.57	589	8
25.39	3.51	774	10
25.95	3.43	618	8
26.50	3.36	353	5
27.79	3.21	2123	28
28.80	3.10	734	10
29.68	3.01	410	5
30.07	2.97	656	9
30.49	2.93	423	6
31.42	2.84	391	5
32.49	2.75	330	4
33.66	2.66	431	6
34.78	2.58	444	6

[000188] The following table presents the X-ray diffraction results of form A+C of **S-1** as depicted in Figure 12D, wherein the diffraction angles of form C were identified:

Mixture Form A with Form C				
Peak Assignment not form A line	**Angle 2-Theta °**	**d value Angstrom**	**Intensity Cps**	**Intensity %**
	5.65	15.6	100	41
certain	6.89	12.8	7	3
	7.43	11.9	8	3
	8.68	10.2	42	17

probable	9.46	9.3	25	10
	9.94	8.9	111	45
	11.20	7.9	7	3
	12.60	7.0	12	5
certain	13.49	6.6	9	4
	14.89	5.95	82	33
	15.17	5.84	22	9
Probable	15.99	5.54	41	17
	16.84	5.26	164	67
	17.21	5.15	64	26
	18.00	4.92	17	7
	18.54	4.78	45	18
	19.37	4.58	27	11
	19.86	4.47	39	16
	20.66	4.29	21	9
	21.79	4.08	46	19
	22.36	3.97	246	100
certain	22.84	3.89	52	21
	23.53	3.78	46	19
	23.91	3.72	38	15
	24.84	3.58	16	7
	25.41	3.50	37	15
	26.15	3.41	14	6
	26.60	3.35	12	5
	27.89	3.20	60	24
	28.86	3.09	31	13
	30.01	2.98	30	12
	30.52	2.93	14	6
	30.98	2.88	13	5
	31.34	2.85	15	6
	32.72	2.73	14	6
	33.93	2.64	15	6
	34.84	2.57	15	6

[000189] In one embodiment form C has additional lines which are overlaid by signals of form A.

[000190] Peak search and d-value calculation were performed with software EVA version 10, 0, 0, 0, Cu Kalpha2 was removed by software, and only lines up to 35° 2theta were listed.

[000191] The sample PP148-P1 was measured on a 0.1 mm sample holder on a PANalytical PW1710 diffractometer.

[000192] The sample PP148-P52 was measured on a 0.1 mm sample holder on a Bruker D8 Advance diffractometer.

[000193] The following table presents the X-ray diffraction results of form D of **S-1** as depicted in Figure Figure 18 (bottom):

Angle	**d value**	**Intensity**	I/Imax

2-Theta °	Angstrom	Cps	
4.42	19.99	17733	100.0
8.48	10.41	3026	17.1
8.80	10.04	1755	9.9
11.35	7.79	4598	25.9
11.76	7.52	805	4.5
12.72	6.96	1462	8.2
13.84	6.39	8635	48.7
14.45	6.13	5597	31.6
14.64	6.05	9445	53.3
15.10	5.86	7013	39.5
16.14	5.49	1644	9.3
16.64	5.32	1678	9.5
16.95	5l.23	2357	13.3
17.41	5.09	484	2.7
17.59	5.04	678	3.8
18.04	4.91	2308	13.0
18.71	4.74	3439	19.4
19.04	4.66	1824	10.3
19.46	4.56	4093	23.1
20.48	4.33	989	5.6
20.84	4.26	7616	42.9
22.15	4.01	5058	28.5
22.78	3.90	1933	10.9
23.15	3.84	3851	21.7
23.47	3.79	2352	13.3
23.88	3.72	5583	31.5
24.74	3.60	10043	56.6
24. 94	3.57	5395	30.4
25.29	3.52	3149	17.8
25.67	3.47	1290	7.3
26.14	3.41	692	3.9
26.46	3.37	1095	6.2
27.80	3.21	2402	13.5
28.32	3.15	1565	8.8
28.64	3.11	998	5.6
28.90	3.09	1212	6.8
29.38	3.04	3295	18.6
29.92	2.98	756	4.3
30.40	2.94	1278	7.2
31.19	2.87	851	4.8
31.86	2.81	1270	7.2
32.49	2.75	775	4.4
32.82	2.73	920	5.2
33.66	2.66	842	4.7
34.50	2.60	977	5.5
35. 80	2.51	638	3.6
36.06	2.49	700	3.9
36.83	2.44	777	4.4
37.16	2.42	698	3.9

38.02	2.36	733	4.1
38.44	2.34	859	4.8
38.97	2.31	844	4.8
39.99	2.52	791	4.5
40.89	2.21	641	3.6
41.30	2.18	515	2.9

Water vapor sorption (humidity chamber)

[000194] The compound was stored in a glass tube under 96% r.h. (relative humidity) in a humidity chamber at room temperature. After different time of storage Raman measurements were conducted using hermetically closed glass tubes. The results are summarized in Table 1:

Table 1:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A			stored in humidified chamber 96% r.h. / 23°C	(powder)
			4 weeks	A + small amount form B'
			9 weeks	A + form B'
			11 weeks	A + approx. 20% form B' (see Fig 17A)
A	water	111 / 5.0	23°C	(suspension)
			sonication 5 min.	(suspension)
			stirred 19 h / 37°C filtered & air dried	B' (see Fig. 17B)
A	water + 5% ethanol v/v	123 / 2.1	23°C	(suspension)
			stirred3 h / 83°C	viscous sticky mass
			cooled to 47°C within 1.5 h filtered & air dried	B'
A	acetic acid / water 1:2 v/v	138 / 2.0	23°C	(suspension)
			stirred 20 h / 23°C filtered & air dried	A (see Fig. 17C)
A	water + 5% acetic acid v/v	105 / 2.0	23°C	(suspension)

			stirred 12 min / 40°C	(suspension)
			sonicated 2 min.	(suspension)
			stirred 17 h / 40°C cooled to R.T. and removed solution	viscous sticky mass B'

Measurement of the approximate solubility

[000195] To determine the approximate solubility at room temperature, the solvent was added in steps to the solid material. After every addition, the sample was well stirred. The addition of solvent was continued until complete dissolution or until 15 ml of solvent was added. The solubility of solid form A and B' at 23 °C is presented in Table 2.

Table 2:

Solvent	Solid form	Solubility (mg/ml)
ethanol	A	> 200
acetone	A	> 200
TBME	A	> 200
ethyl acetate	A	> 200
THF	A	> 200
acetonitrile	A	> 200
dichloromethane	A	> 200
1,4-dioxane	A	> 200
acetic acid	A	> 200
toluene	A	< 6 turbid solution
ethanol / water 3:1 v/v	A	> 200
ethanol / water 1:1 v/v	A	50
ethanol / water 1:3 v/v	A	< 5
ethanol / *n*-heptane 1:1 v/v	A	180
ethanol / *n*-heptane 1:3 v/v	A	50
acetone / *n*-heptane 1:1 v/v	A	> 200
acetone / *n*-heptane 1:3 v/v	A	90
THF / *n*-heptane 1:1 v/v	A	> 200
THF / *n*-heptane 1:3 v/v	A	65
acetonitrile/ toluene 1:1 v/v	A	> 200
acetonitrile / toluene 1:3 v/v	A	170
ethyl acetate / *n*-heptane 1:1 v/v	A	65
ethyl acetate / *n*-heptane 1:2 v/v	A	9

ethyl acetate / *n*-heptane 1:2 v/v	B'	>9 solid form *transformation into* solid form A
ethyl acetate / *n*-pentane 1:2 v/v	A	13
ethyl formate / *n*-pentane 1:2 v/v	A	12
methyl acetate / *n*-pentane 1:2 v/v	A	8
ethyl acetate / *n*-heptane 1:3 v/v	A	< 5 turbid solution

Suspension equilibration experiments

[000196] Suspension equilibration experiments were carried out with 81 -128 mg of the compound. The suspensions were stirred with a magnetic stirrer. The samples obtained after filtration were air dried at ambient temperature for a short time only to prevent possible desolvation of labile hydrates or solvates. The results of the suspension equilibration experiments of solid form A and B' are presented in Table 3.

Table 3:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A	*n*-heptane	108 / 2.0	23°C	(suspension)
			sonicated 5 min.	(suspension)
			stirred 17 h / 37°C filtered & air dried	A (see Fig. 10a)
A	*n*-heptane + 5% ethanol v/v	117 / 2.1	23°C	(suspension)
			sonicated 5 min.	(suspension)
			stirred 18 h / 37°C filtered & air dried	A
B'	ethyl acetate + *n*-heptane 1:2 v/v	81 / 1.7	23°C	(suspension)
			stirred 2 h / 23°C filtered & air dried	A (see Fig. 10b)
A	ethyl acetate + *n*-heptane 1:2 v/v	124 / 2.0	23°C	(suspension)
			stirred 3 days/ 23°C filtered & air dried	A
A	ethyl acetate + *n*-heptane 1:2 v/v	126 / 2.0	+2°C	(suspension)

			stirred 3 days / +2°C filtered & air dried	A
B'	ethyl acetate + *n*-pentane 1:2 v/v	101 / 1.0	23°C	(suspension)
			stirred 22 h / 23°C filtered & air dried	A (see Fig. 13c)
A	ethyl acetate + *n*-pentane 1:2 v/v	128 / 2.0	23°C	(suspension)
			stirred 20 h / 23°C filtered & air dried	A (see Fig. 10d)
A	ethyl formate + *n*-pentane 1:2 v/v	112 / 2.0	23°C	(suspension)
			stirred 20 h / 23°C filtered & air dried	A (see Fig. 10e)
A	methyl acetate + *n*-pentane 1:2 v/v	126 / 2.0	23°C	(suspension)
			stirred 20 h / 23°C filtered & air dried	A (see Fig. 10f)

Vapor diffusion experiments

[000197] Vapor diffusion experiments were carried out with solution of the compound in different solvents. The solutions were placed in small, open containers that were stored in larger vessels containing miscible, volatile antisolvents. The larger vessels were then tightly closed. The antisolvents diffused through the vapor phases into the solutions, and saturation or supersaturation was achieved. The results of the vapor diffusion experiments of solid form A and B' are presented in Table 4.

Table 4:

Solvent	Antisolvent	Concentration mg / ml	Conditions	Form produced
ethanol	*n*-hexane	204 mg P1 0.4 ml solvent	vapor diffusion, 23°C, 7 days, removed solution	viscous sticky mass
acetone	*n*-hexane	210 mg P1 0.5 ml solvent	vapor diffusion, 23°C, 7 days, removed solution	viscous sticky mass
TBME	*n*-hexane	205 mg P1 0.6 ml solvent	vapor diffusion, 23°C, 7 day, removed solution	viscous sticky mass

ethyl acetate	*n*-hexane	206 mg P1 0.6 ml solvent	vapor diffusion, 23°C, 2 days, filtered and air-dried	**very similar to A**
THF	*n*-hexane	212 mg P1 0.6 ml solvent	vapor diffusion, 23°C, 7 days, removed solution	viscous sticky mass
toluene	*n*-hexane	44 mg P1 2.0 ml solvent	vapor diffusion, 23°C, 2 days, removed solution	**very similar to A** (see Fig. 11A)
dichloromethane	*n*-hexane	204 mg P1 1.6 ml solvent	vapor diffusion, 23°C, 2 days, removed solution	**very similar to A**
1,4-dioxane	*n*-hexane	215 mg P1 0.5 ml solvent	vapor diffusion, 23°C, 7 days, removed solution	viscous sticky mass
acetic acid	water	219 mg P1 0.3 ml solvent	vapor diffusion, 23°C, 7 days, removed solution	**very similar to A** (see Fig. 11B)
acetonitrile	water	212 mg P1 0.4 ml solvent	vapor diffusion, 23°C, 6 days, removed solution	viscous sticky mass

Evaporation experiments

[000198] Solutions of the compound were dried at room temperature (dry nitrogen flow) without stirring. The results of the evaporation experiments of solid form A are presented in Table 5.

Table 5:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A	ethanol	100 / 2.0	23°C	(solution)
			evaporated(dry N2) 2 days / 23°C	B"
A	ethyl acetate	109 / 2.0	23°C	(solution)
			evaporated (dry N_2) 1 day / 23°C	very similar to A (see Fig 12A)
A	THF	183 / 2.0	23°C	(solution)
			evaporated (dry N_2) 5 days/ 23°C	A + C (see Fig. 12B)

Precipitation experiments

[000199] Precipitation experiments were carried out with 42 - 79 mg of the compound. The non-solvent was added to the solution. The samples obtained after filtration (glass filter porosity P4)

were air dried at ambient temperature and for a short time only to prevent possible desolvation of labile hydrates or solvates. The results of the precipitation experiments of solid form A are presented in Table 6.

Table 6:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A	ethanol	79 / 0.2	23°C	(solution)
		79 / 1.2	added of 1.0 ml n-heptane	(phase separation)
			stored 11 weeks / -20°C; removed solution and dried solid residue (N_2 43 ml/min) 50 min R.T.	very similar to A
A	ethyl acetate	42 / 0.2	23°C	(solution)
		42 / 1.2	added of 1.0 ml n-heptane	(viscous sticky mass)
			stirred 14 h / 40°C filtered & air dried	A
A	THF	62 / 0.2	23°C	(solution)
		62 / 1.2	added of 1.0 ml n-heptane	(viscous sticky mass)
			stirred 14 h / 40°C filtered & air dried	A
A	dichloromethane	75 / 0.3	23°C	(solution)
		75 / 1.2	added of 1.0 ml *n*-heptane	(viscous sticky mass)
			stirred totally 13 h / 40°C filtered & air dried	A

Recrystalization from solution

[000200] The compound was dissolved in different solvent systems at room temperature and cooled to +5°C or to -20°C. The samples obtained after filtration (glass filter porosity P4) were air dried at ambient temperature for a short time only to prevent possible desolvation of labile hydrates or solvates.

[000201] The results of the recrystalization experiments of solid form A are presented in Table 7.

Table 7:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A	ethanol + *n*-heptane 1:1 v/v	72 / 0.4	23°C	(solution)
			stored 4 weeks / +5°C; filtration, washed (*n*-heptane) and air-dried	A
A	ethyl acetate + *n*-heptane 1:1 v/v	80 / 1.2	23°C	(solution)
			stored 4 weeks / -20°C; filtered and air-dried	very similar to A (see Fig. 13A)
A	acetonitrile + toluene 1:1 v/v	91 / 0.2	23°C	(solution)
			stored 4 weeks / -20°C; removed solution and dried solid residue (N_2 43 ml/min) 212 min R.T.	very similar to A
A	ethanol + *n*-heptane 1:3 v/v	52 / 0.4	23°C	(solution)
			stored 1 day / +5°C; filtered, washd (*n*-heptane) and air-dried	A
A	acetonitrile + toluene 1:3 v/v	65 / 0.4	23°C	(solution)
			stored 4 weeks / -20°C; filtered and air-dried	very similar to A (see Fig. 16B)

Freeze drying experiment

[000202] The compound was dissolved in 1,4-dioxane and the solution was cooled to -50°C. During sublimation of the solvent the temperature of the solid was < 0°C. as presented in Table 8:

Table 8:

Starting form	Solvent	Concentration mg / ml	Conditions	Form produced
A PP148-P1	1,4-dioxane	**102 / 2.0**	23°C	(solution)
			freeze dried <0°C	viscous sticky mass
			stored 12 days / R.T.	**very similar to A** (see Fig. 14)

Drying Experiment

[000203] The sample was dried overnight in a dry N_2-atmosphere at room temperature before closing the DSC sample pan.

[000204] The results are summarized in Table 9:

Table 9:

Starting form	mg	Conditions	DSC
B'	3.6 mg	dried overnight 23°C (mass loss 1.0%)	Fig. 15

Cooling and reheating of the melt experiments

[000205] After heating in DSC to 120°C the samples were cooled to -50°C and reheated to 120°C. The results are summarized in Table 10:

Table 10:

Starting form	mg	Conditions	DSC
A	3.4 mg	fast cooled to -50°C, heated: -50°C to 120°C / 20 K/min, fast cooled to -50°C heated again: -50°C to 120°C / 20 K/min	Fig. 7A
A PP148-P2	4.4 mg	fast cooled to -50°C heated: -50°C to 120°C / 20 K/min fast cooled to to -50°C C heated again: -50°C to 120°C / 20 K/min	Fig. 7B
A	3.4 mg	fast cooled to -50°C heated: -50°C to 120°C / 20 K/min fast cooled to -50°C C heated again: -50°C to 120°C / 20 K/min	Fig. 7C
B'	2.9 mg	fast cooled to -50°C heated: -50°C to 120°C / 20 K/min fast cooled to -50°C heated again: -50°C to 120°C / 20 K/min	Fig. 7D

Relative stability experiments

[000206] Suspension experiments were carried out with 130 -145 mg of the compound. The suspensions were stirred with a magnetic stirrer and filtered after a predefined time. The samples obtained after filtration (glass filter porosity P4) were air dried at ambient temperature. The results are summarized in Table 11:

Table 11:

Starting forms	Solvent	Concentration mg / ml	Conditions	Form produced
A	ethyl acetate / n-heptane 1:2 (v/v)	approx. 130 / 2.0	23°C	(suspension)
			stirred 3 days / 23°C; filtered and air-dried	A (see Fig. 16A)
A	ethyl acetate / n-heptane 1:2 (v/v)	(81 + 64) / 2.0	23°C	(suspension)
			stirred 1 day / 23°C; filtered and air-dried	A (see Fig. 16B)

Water solubility of solid forms A and B'

[000207] Suspensions of the solid forms (25 or 50 mg in 3.5 or 7.0 ml bidistilled water) were shaken (800 rpm) and filtered after 0.5 h, 1.5 h, 4 h and 20 h. After filtration the solid residue was checked by Raman spectroscopy and the concentration in the clear solution was determined by HPLC.

[000208] The solubility of solid form A of **S-1** in water at 22 °C is summarized in Table 12:

Table 12:

Suspension equilibration time [h]	Solubility[a] [mg/1000ml]	Solid residue[b]
0.5	21.0 ± 3.9	A + B' (approx. 95% + 5%)[c]
1.5	24.0 ± 1.4	A + B' (approx. 90% + 10%)[c]
4.0	27.6 ± 1.5	A + B' (approx. 85% + 15%)[c]
20	24.5 ± 1.7[d]	A + B' (approx. 75% + 25%)[c]

a) Mean value of two measurements (± standard deviation)
b) Raman measurements
c) Rough estimate
d) pH of the solution : 8.7

[000209] The solubility of Form B' of **S-1** in water at 22 °C is summarized in Table 13:

Table 13:

Suspension equilibration time [h]	Solubility[a] [mg/1000ml]	Solid residue[b]
0.5	27.4 ± 0.9	B'
1.5	27.3 ± 0.8	B'
4.0	25.6 ± 0.1	B'
20	26.7 ± 0.3[c]	B'

a) Mean value of two measurements (± standard deviation)
b) Raman measurements
c) Rough estimate
d) pH of the solution : 8.7

Characterization of S-1–P1 Form A

[000210] The starting material for the polymorphism study, batch no. ***S-1–P1***, is crystalline and the crystal form A. TG-FTIR shows that the mass loss up to 200°C is very low (< 0.2%) and therefore batch no. ***S-1 –P1*** is not a hydrate or solvate. Batch no. ***S-1 –P1*** melts at 82°C (DSC peak temperature, heating rate 20 K/min). After melting and fast cooling to -50°C in DSC the anhydrous liquid crystal form was produced. The sample showed a phase transition temperature of approx. 52°C and did not recrystallize during heating in DSC. ***S-1 –P1*** might contain a small amount (roughly estimated 5%) of form B' or B".

[000211] The DVS measurement of form A at 25°C does not show any evidence of classical hydrate formation under the experimental conditions used. The maximum water content at 93% relative humidity. is 1.5%. The very slight hysteresis is most probably caused by a viscous layer (possibly consisting of solid form B') on the surface of the particles, which influences the rate of water exchange. In fact, after storing form A at 96% relative humidity at room temperature for 11 weeks, Raman spectroscopy and DSC indicated the formation of approx. 20% of form B'.

Characterization of solid form B'

[000212] Investigations by DSC and XRPD indicate that the solid form produced during storage of solid form A at 40°C and 75% relative humidity. (batch S-1-P4; 40°C / 75%RH) is a paracrystalline form, having limited low-range order. This limited order most probably is responsible for the endothermal peak in DSC around 55°C and the broad shoulder around 17° in the diffraction pattern. The solid form of batch S-1-P4 40°C / 75% relative humidity is Form B'.

[000213] The DVS behavior of solid form B' at 25°C is not the typical sorption behavior of a hydrate. The maximum water content at 94% relative humidity. is approx. 2.4%. Even though a certain hysteresis is observed, there is no clear step in the sorption curve which would clearly indicate the existence of a classical hydrate.

Formation of solid form B'

[000214] In addition to the observed transformation at high relative humidity, solid form B' can be produced by stirring a suspension of solid form A in water at 37°C overnight.

Formation of solid form B"

[000215] Pathways to produce solid form B" are melting and cooling of the melt, and slow

evaporation of solutions in solvents such as ethanol. Polymorph B" can be prepared from polymorphs A and D by heating them to above their respective melting points of 80°C and 130°C. B' and B" are not distinguishable from any analytical methods used thus far but are distinguished based on their routes of formation. B' is assigned as a lyotropic liquid crystalline form due to its solvent mediated formation while B" is assigned as a thermotropic liquid crystalline form from its thermal method of preparation. Evaporation of the drug from solvents such as ethanol without an antisolvent also produces B".

Formation of solid form C

[000216] Polymorph C can only be obtained as a mixture with A by dissolving and subsequently evaporating the drug out of THF at ambient temperature.

Formation of solid form D

[000217] Polymorph D was originally produced by crystallization from a solvent/antisolvent mixture at 50°C using ethyl acetate and cyclohexane as the solvent and antisolvents respectively. Form D can also be prepared from other polymorphic forms by "seeding" the sample with a small amount of D and storing it at 110°C/0%RH for 7 days or at 50°C in water for 24 hours and drying.

Formation of solid form toluene solvate

[000218] The toluene solvate was prepared by any solvent/antisolvent crystallization method that used toluene as the antisolvent.

Water solubility of solid forms A and B'

[000219] The solubility of forms A and B' of compound **S-1** in water at 22°C are 24.0 ± 1.4 mg /1000 ml and 27.3 ± 0.8 mg /1000 ml, values obtained after 1.5 h suspension equilibration time. These solubilities are very similar because of the fast transformation of form A into form B' on the surface of the particles during the solubility experiments.

Characterization of different batches of solid form A

[000220] Samples of batches S-1-P1, S-1-P2 and S-1-P3 show the same diffraction pattern. DSC measurements show that they most probably contain several % of solid form B' or B", indicated by heat capacity changes around 50°C. Sample S-1-P2 shows the highest level of solid form B' or B" (approx 20%). To better understand the DSC results, scanning electron micrographs (SEM) of samples S-1-P1 and S-1-P2 were produced. Whereas the pictures of sample S-1-P1 show quite well-formed particles, the pictures of sample S-1-P2 show a partial transformation, possibly caused by too high a drying temperature or partial contact with water. The partial formation of solid form B' or B" could also be caused by fast precipitation and a relatively high antisolvent /

solvent ratio after precipitation. Other explanations would be drying at high temperatures or storage under high humidity conditions.

Solvent systems for crystallization of solid form A

[000221] Crystal form A is highly soluble in a number of solvents commonly used for crystallization. Due to its high solubility, solvent / antisolvent mixtures are necessary for crystallization.

[000222] Suspension equilibration experiments at room temperature revealed that solid form B' (batch S-1-P4; 40°C / 75%RH) can be transformed into solid form A when stirring suspensions in ethylacetate / heptane 1:2 v/v or ethylacetate / pentane 1:2. In addition, suspension equilibration experiments using solid form A in ethyl formate / pentane 1:2 v/v and methyl acetate / pentane 1:2 v/v showed no transformation of solid form A. Therefore, these class 3 solvent / antisolvent mixtures can be used for crystallization of form A. The advantages of these solvent systems are the significantly lower boiling temperatures and therefore the possibly lower drying temperatures.

[000223] The details of the characterization of S-1-P1, solid Form A are given in Table 14:

Table 14:

Compound	**S-1**	
Batch no.	S-1-P1	
XRPD	• solid form A	Figures XRPD-1a and XRPD-1b (see Figure 4A)
Raman	• solid form A • sample might contain a small amount of B' or B"	Figure Raman-1 (see Figure 5A)
TG-FTIR	• mass loss 25°C to 245°C: < 0.2%	Figure TG-FTIR-1 (see Figure 6A)
DSC	• melting temperature: 82.4°C (peak temperature, hermetically sealed gold sample pan, heating rate 20 K/min) • AH: -42 J/g • sample might contain a small amount (roughly estimated 5%) of form B' or B"	Figures DSC-1a and DSC-1b (See Figure 7A)
SEM	• quite well-formed particles	Figures SEM-1 (see Figure 8A
DVS	• water content at 50% r.h.: 0.4% • maximum water content at 93% r.h.: 1.5%	Figures DVS-1a and DVS-1b (Figure 9A

[000224] The details of the characterization of S-1-P2, solid Form A, are given in Table 15:

Table 15:

Compound	**S-1**
Batch no.	S-1-P2

XRPD	• solid form A	Figures XRPD-2a and XRPD-2b (see Figure 4B)
Raman	• solid form A + B' or B"	Figure Raman-2 (See Figure 5B)
TG-FTIR	• mass loss 25°C to 245°C: < 0.2%	Figure TG-FTIR-2 (see Figure 6B)
DSC	• melting temperature: 85.4°C (peak temperature, hermetically sealed gold sample pan, heating rate 20 K/min) • AH: -43 J/g • sample contains approx. 20% of form B' or B"	Figures DSC-2a and DSC-2b (see Figure 7B)
SEM	• pictures show partial transformation	Figures SEM-2 (see Figure 8B)
DVS	• water content at 50% r.h.: 0.3% • maximum water content at 95% r.h.: 0.6%	Figures DVS-2a and DVS-2b (see Figure 9B)

[000225] The details of the characterization of S-1-P3, solid Form A, are given in Table 16:

Table 16:

Compound	**S-1**	
Batch no.	S-1-P3	
XRPD	• solid form A	Figures XRPD-3a and XRPD-3b (see Figure 4C)
Raman	• solid form A • sample might contain a small amount of B' or B"	Figure Raman-3 (see Figure 5C)
TG-FTIR	• mass loss 25°C to 245°C: < 0.2%	Figure TG-FTIR-3 (see Figure 6C
DSC	• melting temperature: 84.4°C (peak temperature, hermetically sealed gold sample pan, heating rate 20 K/min) • AH: -42 J/g • sample might contain a small amount (roughly estimated 5%) of form B' or B"	Figures DSC-3a and DSC-3b (see Figure 7C
SEM	-not analyzed	-
DVS	-not analyzed	-

[000226] The details of the characterization of S-1-P4, solid Form B' are given in Table 17:

Table 17:

Compound	**S-1**
Batch no.	S-1-P4 40°C / 75%RH

XRPD	• solid form B' • sample might contain a small amount of form A	Figures XRPD-4a and XRPD-4b (see Figure 4D)
Raman	• solid form B'	Figure Raman-4 (see Figure 5D)
TG-FTIR	• mass loss 25°C to 245°C: 1.0% (water)	Figure TG-FTIR-4 (see Figure 6D)
DSC	• endothermal peak: ~ 55°C (peak temperature, hermetically sealed gold sample pan, heating rate 20 K/min) • AH:~10J/g	Figures DSC-4a and DSC-4b (see Figure 7D)
SEM	• significant change in morphology	Figures SEM-3 (see Figure 8C)
DVS	• water content at 50% r.h.: ~ 0.8% • maximum water content at 94% r.h.: ~ 2.4%	Figures DVS-3a and DVS-3b (see Figure 9C)

[000227] The different batches P1, P2 and P3 of compound **S-1** revealed crystalline Form A with similar characteristic behavior of XRPD, Raman, TG FTIR , DVS and DSC results. Batch P4 revealed a paracrystalline solid form as characterized by its broad XRPD, Raman, TG FTIR , DVS and DSC results as described hereinabove.

Relative Stability of Polymorphic Forms under Dry Conditions

[000228] The DSC thermogram of A and D in figure 19 show that A melts near 80°C while D has a melting point near 130°C. The enthalpy of melting for A is 40 ±5 J/g while the enthalpy of melting is 75 ±5 J/g. The melting temperature and enthalpy suggest that D possesses greater stability in comparison to form A.

[000229] Figure 17D shows that melting of polymorphs A or D produces the liquid crystalline B" polymorph instead of a truly isotropic liquid phase. Formation of a true liquid phase was not observed even after heating the sample to 200°C. Cooling the B" polymorph to ambient temperature does not result in recrystallization back to form A or D. This is verified by the absence of a melting endotherm in the DSC curve (Fig. 17D) of the sample reheated after it was melted then subsequently cooled to ambient temperature. The DSC curve also shows that the B" form undergoes a phase transition near 55°C. Similar glass transitions are observed for B', which along with the broad shoulder around 17° in figure 4D are the basis for their designation as liquid crystalline phases. The XRPD displays harmonic peaks for B', along with the broad shoulder around 17° in figure 4D which are the basis for their designation as liquid crystalline phases.

[000230] Figure 17e shows that heating of polymorphs A and B" to 110°C in the presence of D causes the A and B" forms to rearrange into D. This confirms that the A and B" are metastable phases below 130°C that can be converted to form D. However, likely due to the high energetic barrier for the transition, the rates of conversion of A or B" to D are very slow without any D present initially to seed the crystallization. Thus forms A and B" can be considered to be

practically stable at ambient temperature. Above 130°C, form D melts and changes to B" which now becomes the most stable form. Micronization of the polymorph A particles under dry conditions also produced ~25% conversion to B".

Relative Stability of Polymorphic Forms under Humid Conditions

[000231] Polymorph A stays stable in its A form for at least 7 days under storage conditions of ambient temperature/75%RH (Relative Humidity), ambient temperature/100%RH, 30°C/75%RH and 50°C/0%RH. But it converts to B' when stored at 50°C/75%RH. Some of the results are shown in figure 17F. In fact, polymorph A stored at 25°C/60%RH and 30°C/65%RH were stable through 36 months and 9 months respectively while a sample stored at 40°C/75%RH converted to B' within one month. These results indicate that polymorph A converts to B' in the presence of moisture.

[000232] Polymorph D on the other hand, remains stable at 50°C/75%RH as well as the other conditions of ambient/75%RH, ambient/100%RH, 30°C/75%RH and 50°C/0%RH. In fact, polymorph D in the presence of moisture acts as the seed for the crystallization process and drives the transformation of polymorphs A and B' into D, similar to its role in seeding the A to D crystallization in dry conditions. Figure 17G(a) shows the time evolution of polymorph A seeded with a small amount of D at 50°C/75%RH. The amount of polymorph D initially added to the sample is very small that it isn't detectable by the DSC with heating rate of 10°C/min. After 24 hours, most of the polymorph form A has been converted to B' but a small amount of sample has also been converted to D and the amount of sample in D increases over time. The transformation process is speeded up in Figure 17G(b) by storing the sample in water at 50°C. Form A has been converted to both B' and D after 6 hours but the sample is predominantly in form D by 24 hours. This is in contrast to the conversion to B' of the pure A form which doesn't convert further to D. It is yet unclear if A can convert to D directly with seeding in water or if it only converts to B' (which subsequently converts to D in water). Further work has shown that the A and B' convert to D in the presence of moisture at lower temperatures also albeit at slower rates.

Relative stability of toluene Solvate in toluene

[000233] Recrystallization of **S-1** from a solvent/antisolvent system that uses toluene as the antisolvent produces the toluene solvate. Toluene solvate has a melting point near 100°C with the enthalpy of melting 70±5 J/g. TGA graph of the toluene solvate in Figure 20 shows that the toluene content in the solvate is ~7% which corresponds to one toluene molecule for every three molecules of S-1. The solvent/drug mass ratio stayed the same for each sample batch prepared and suggests that the toluene molecules reside inside the unit cell structure rather than in channels or layers outside the lattice. Owing to the low solubility of S-1 in toluene (< 2mg/mL), no noticeable transformation from form D to the toluene solvate was observed after suspension

(50mg/mL) in toluene for 4 days both at ambient temperature and 50°C. Sonication of the suspension for 10 minutes did produce partial transformation to the toluene solvate.

[000234] It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow:

CLAIMS

1. A crystalline form of an (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide compound (form A), characterized by:

   an X-ray powder diffraction pattern displaying peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 8.6 (10.3), 9.9 (8.9), 12.4 (7.1), 15.0 (5.9), 16.7 (5.3), 17.3 (5.1), 18.0 (4.9), 18.5 (4.8), 19.3 (4.6), 19.8 (4.5), 20.6 (4.3), 21.8 (4.1), 22.3 (4.0), 23.4 (3.8), 23.9 (3.7), 24.6 (3.6), 24.9 (3.6), 25.4 (3.5), 26.0 (3.4), 26.5 (3.4), 27.8 (3.2).

2. The crystalline form of claim 1, wherein said crystalline form is an anhydrous crystalline form.

3. The crystalline form of claim 1, wherein said crystalline form is characterized by the characteristics listed in (a) and a melting point of about 82°C.

4. The crystalline form of claim 1, wherein said crystalline form is characterized by an X-ray powder diffraction pattern as depicted in Figure 4a.

5. A solid composition comprising a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide of claim 1, and a suitable carrier or diluent.

6. The composition of claim 5, wherein said crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide is an anhydrous crystalline form.

7. A process for the preparation of a crystalline form of (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide of claim 1, said process comprising dissolving *amorphous* (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-

methylpropanamide in at least one organic solvent at a temperature of between about -20°C to +5°C under conditions permissive to crystallization, thereby obtaining said crystalline form.

8. The process of claim 7, wherein said organic solvent comprises a mixture of a solvent and an antisolvent.

9. The process of claim 8, wherein said mixture comprises ethyl formate and *n*-pentane in a 1:2 v/v ratio.

10. The process of claim 8, wherein said mixture comprises methyl acetate and *n*-pentane in a 1:2 v/v ratio.

11. A solid composition comprising a mixture of a crystalline form of a (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide of claim 1 and a paracrystalline form of a (*R*) or (*S*)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide, and a suitable carrier or diluent, and whereby said paracrystalline form is characterized by:
    a. an X-ray powder diffraction pattern displaying a broad halo with two harmonic peaks between 15-25 °2θ and
    b. a phase transition point of about 55°C as determined by differential scanning calorimetry (DSC).

12. The crystalline form of claim 1, wherein said crystalline form is characterized by an X-ray powder diffraction pattern as containing the identification peaks at °2θ (d value Å) angles of about 5.6 (15.9), 7.5 (11.8), 9.9 (8.9), and 12.4 (7.1).

13. Use of crystalline form A as defined in claim 1, in the preparation of a medicament for treating a hormone-related condition selected from androgen decline in aging male (ADAM), androgen decline in female (ADIF), and chronic muscular wasting.

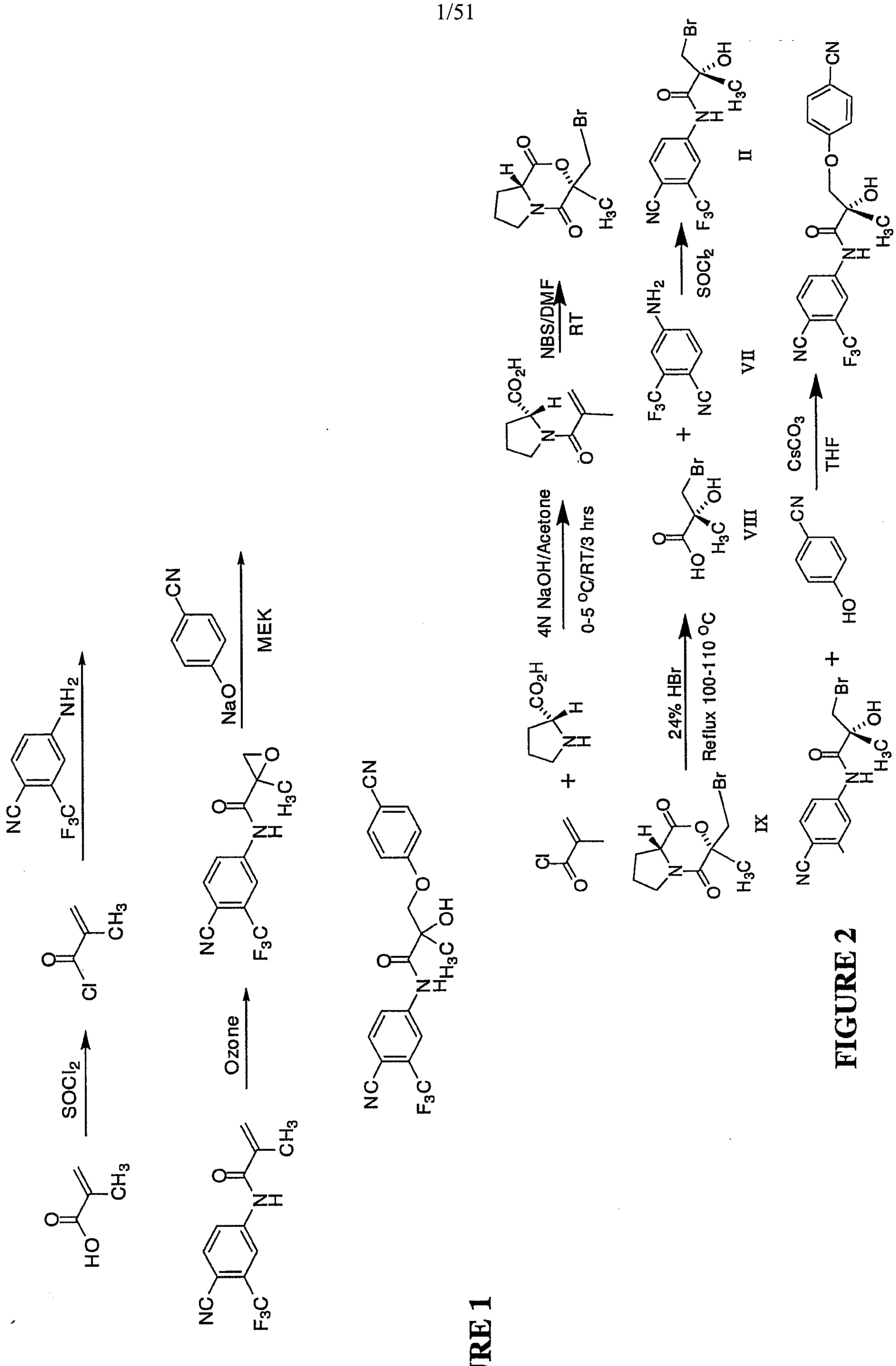


FIGURE 1

FIGURE 2

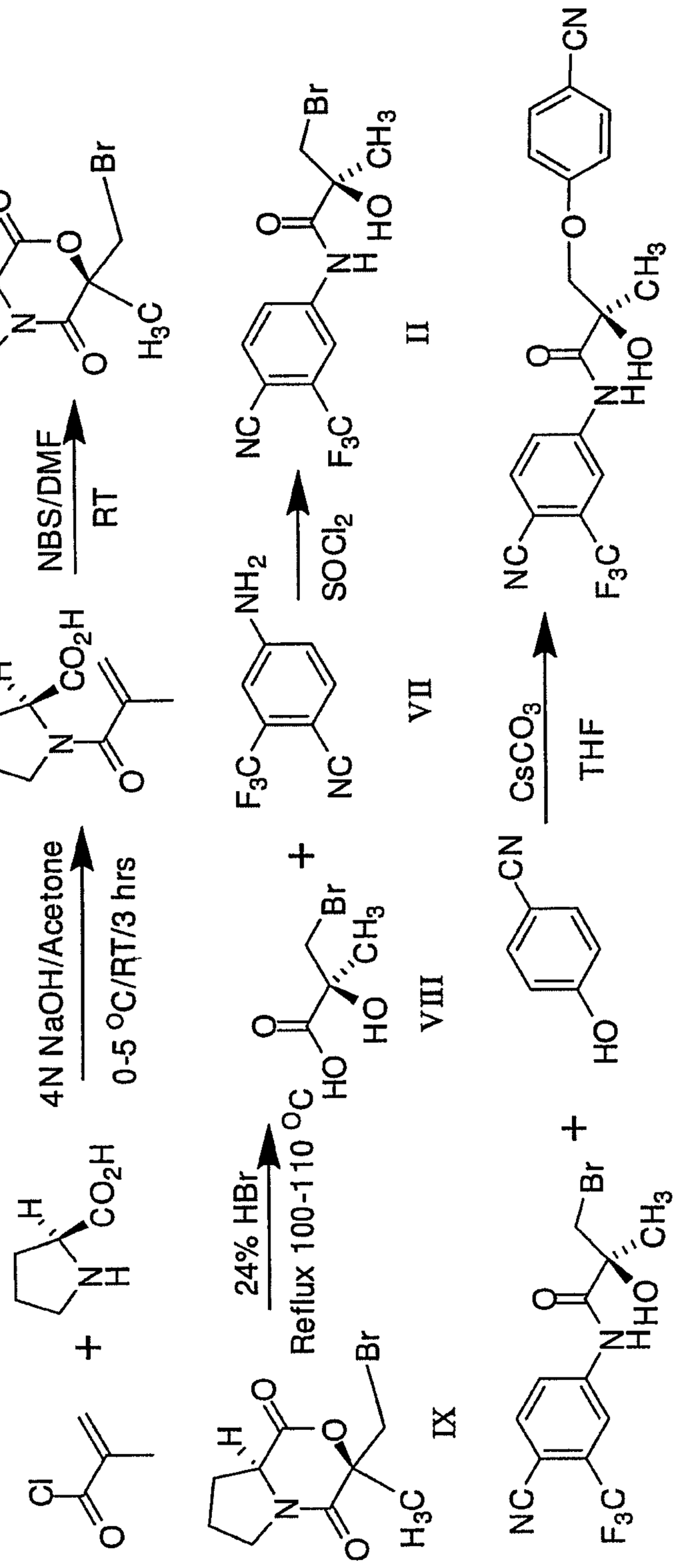

CN
Br
O
H
O
N
O
H3C
NBS/DMF
RT
CO2H
H
N
O
NH2
F3C
NC
SOCl2
II
VII
Br
CH3
HO
O
N
H
NC
F3C
CsCO3
THF
4N NaOH/Acetone
0-5 °C/RT/3 hrs
24% HBr
Reflux 100-110 °C
VIII
HO
IX
Cl
O

FIGURE 3

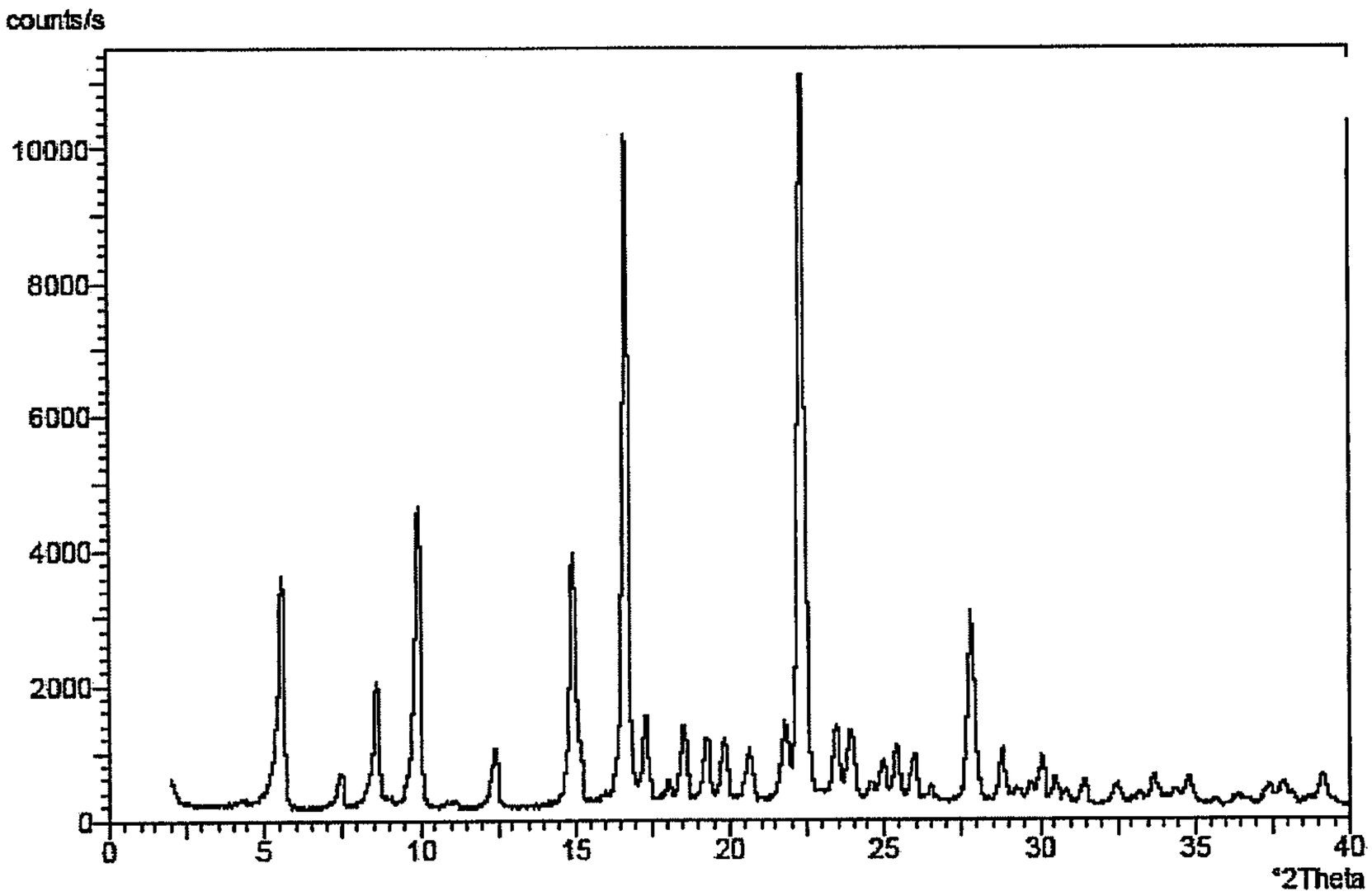

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15
20
25
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35
40
°2Theta

FIGURE 4A

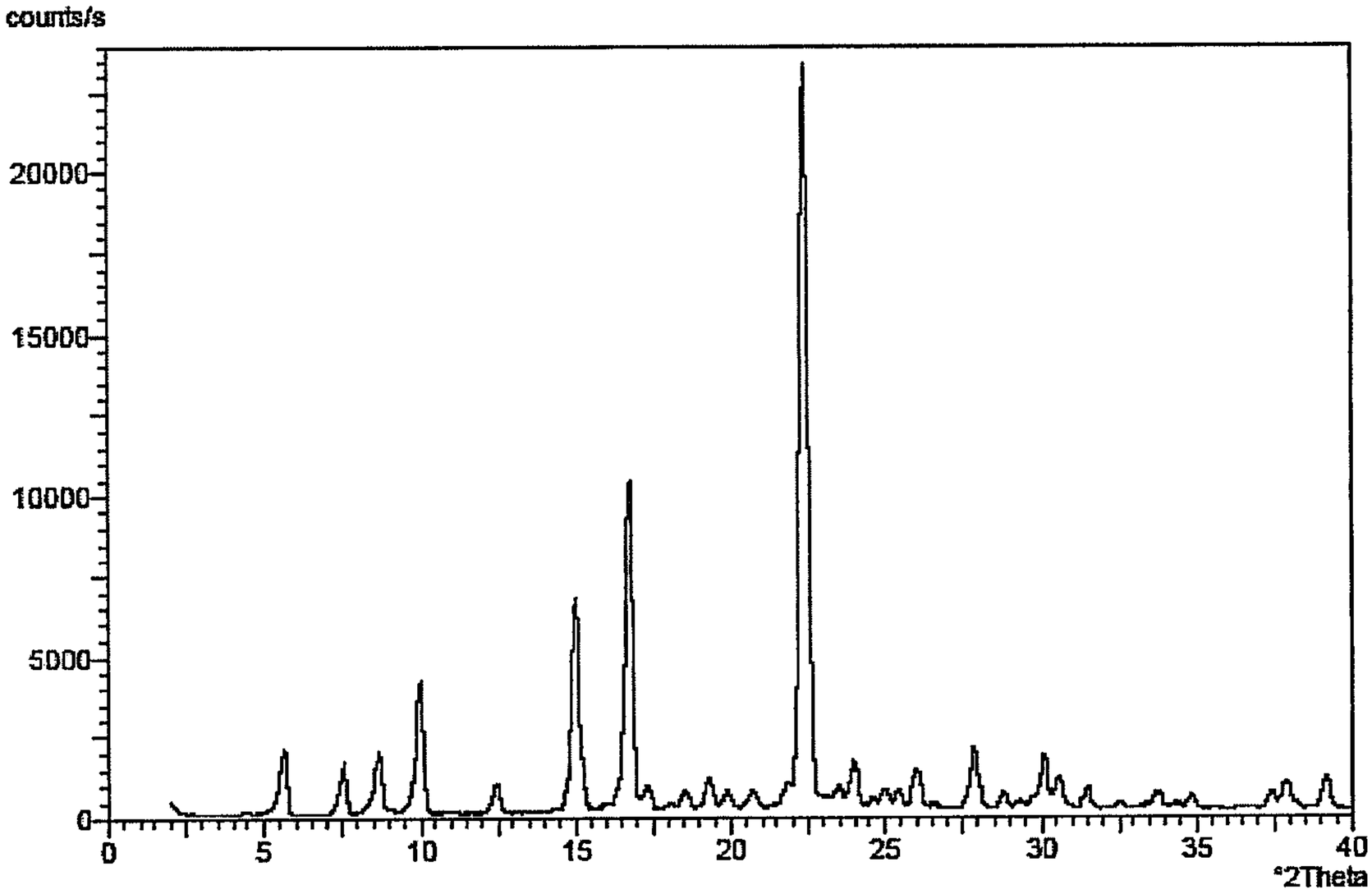


FIGURE 4B

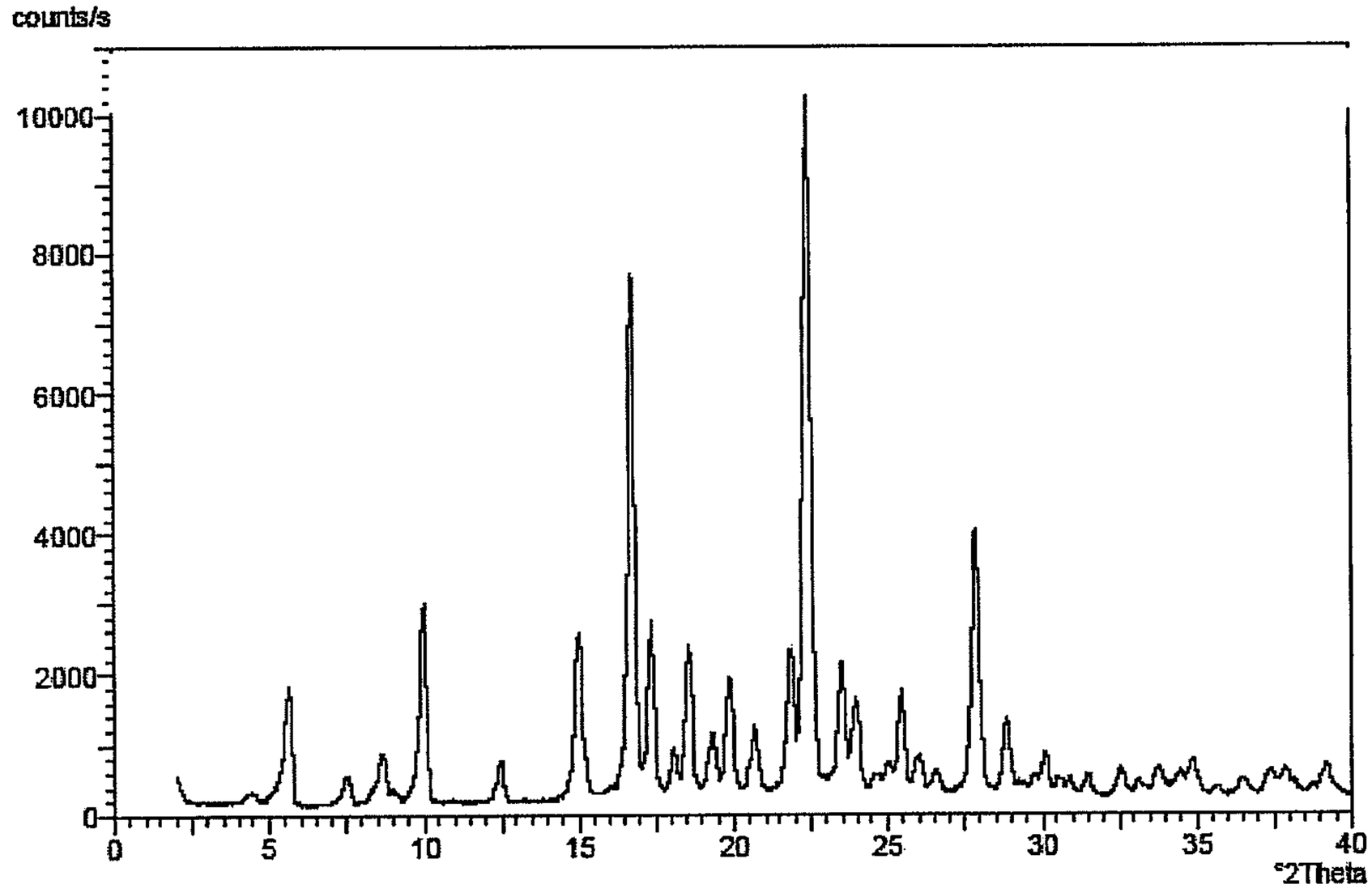

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°2Theta

FIGURE 4C

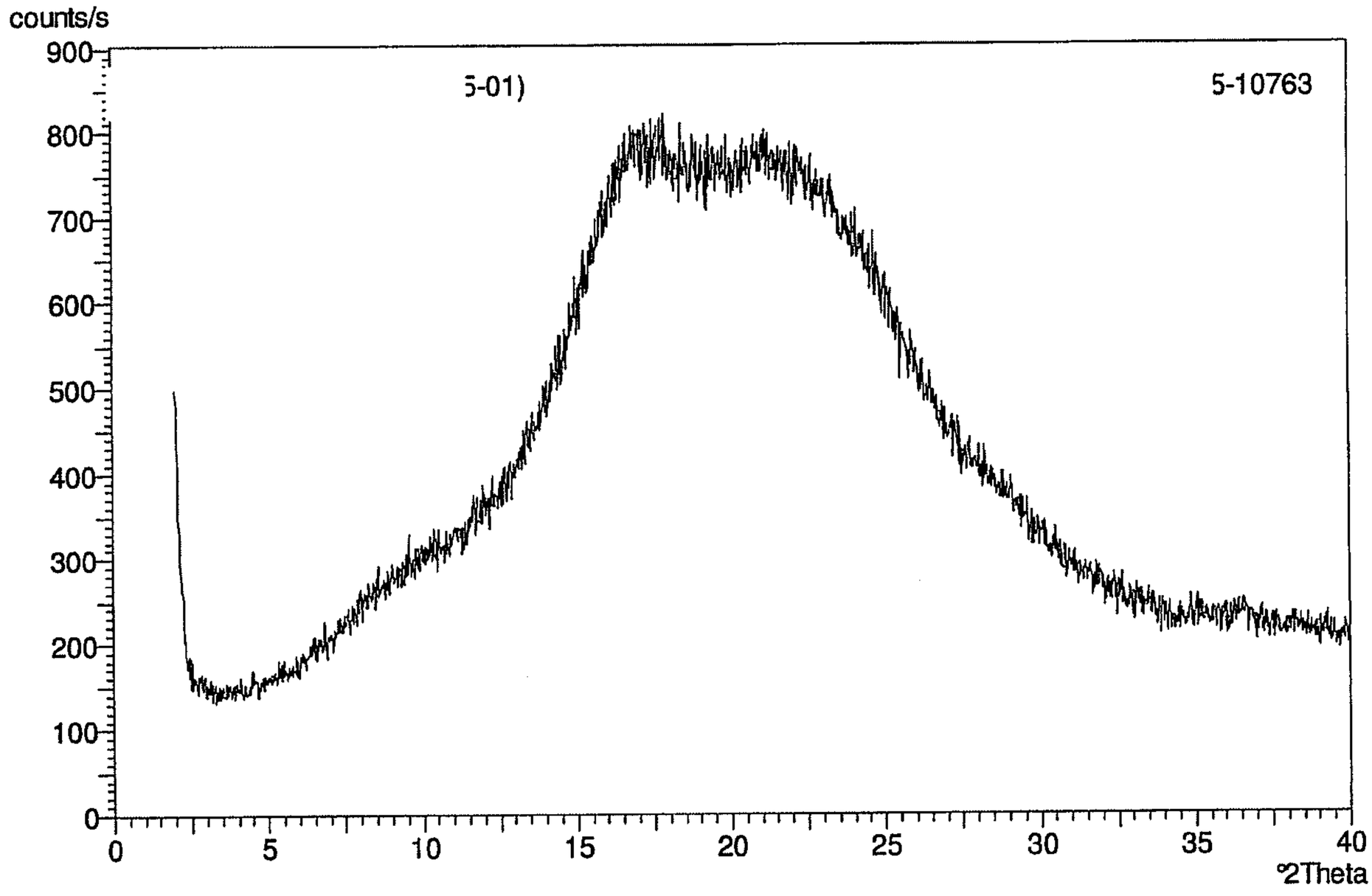

counts/s
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800
700
600
500
400
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200
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0
5-01)
5-10763
0
5
10
15
20
25
30
35
40
°2Theta

FIGURE 4D

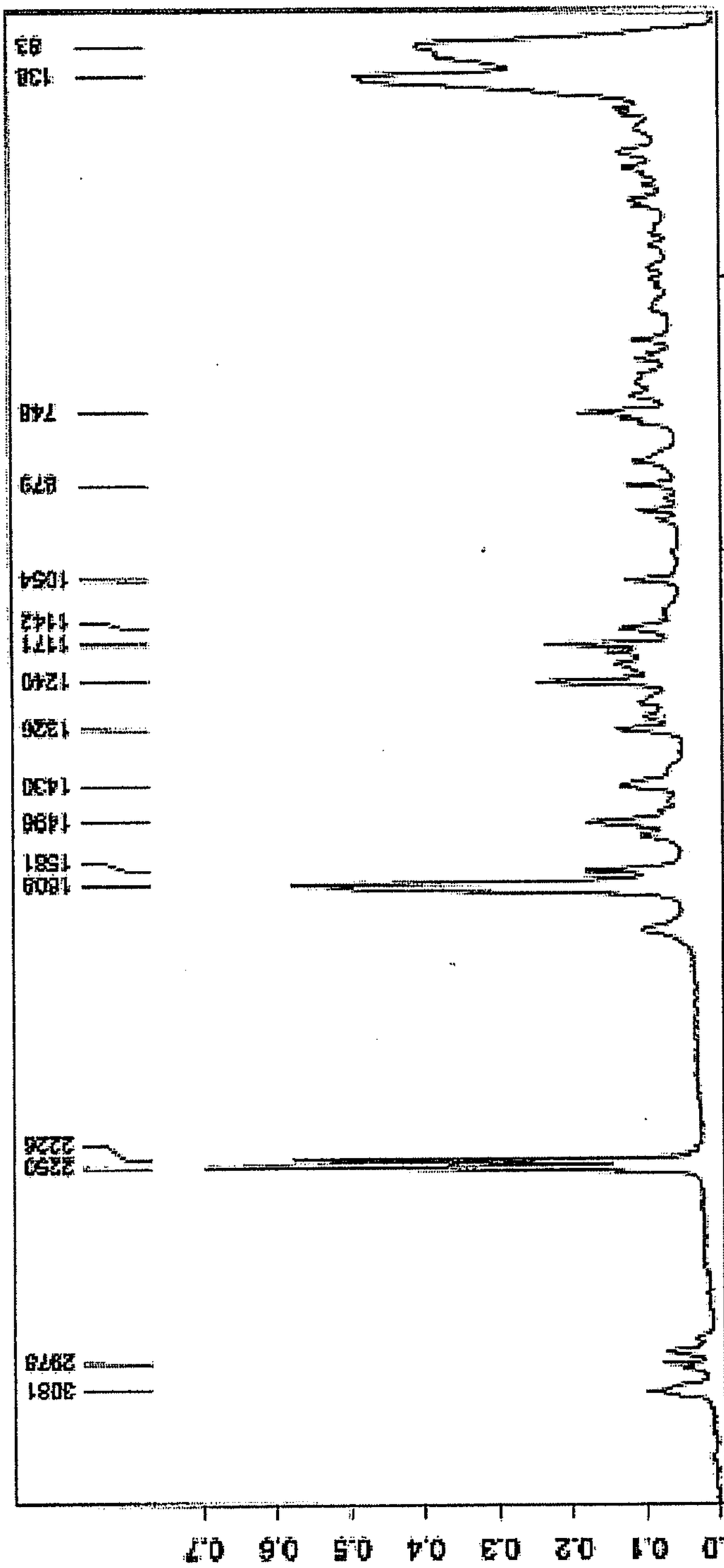

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138
748
879
1054
1142
1171
1240
1329
1430
1496
1581
1609
2236
2250
2879
3081
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3500
3000
2000
1500
1000
500
Wavenumber cm-1

FIGURE 5A

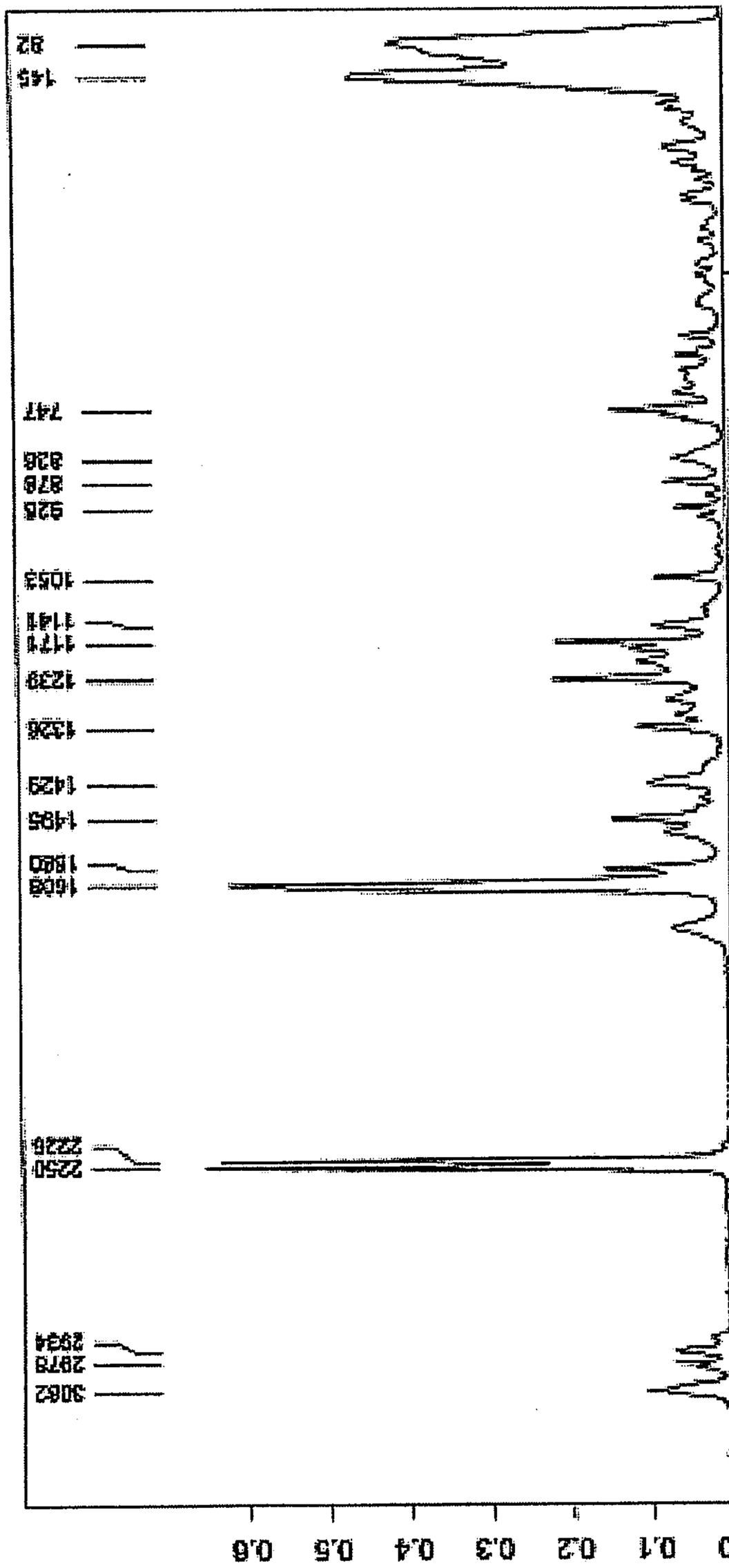

3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
3062
2978
2934
2250
2226
1608
1580
1495
1429
1326
1239
1177
1141
1053
926
878
826
747
82
145

FIGURE 5B

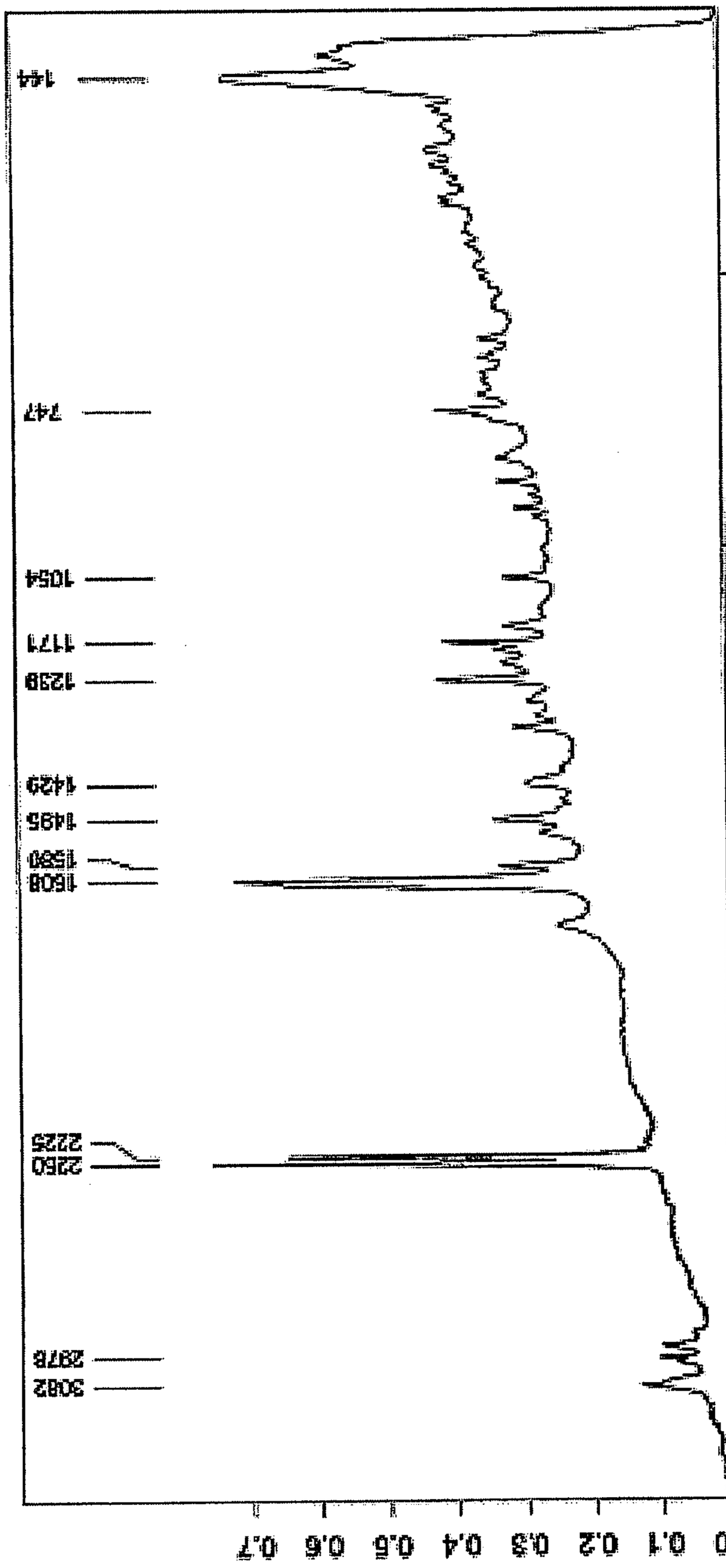

1424
747
1054
1171
1239
1429
1495
1580
1608
2260
2225
2878
3082
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3500
3000
2500
2000
1500
1000
600
Wavenumber cm-1

FIGURE 5C

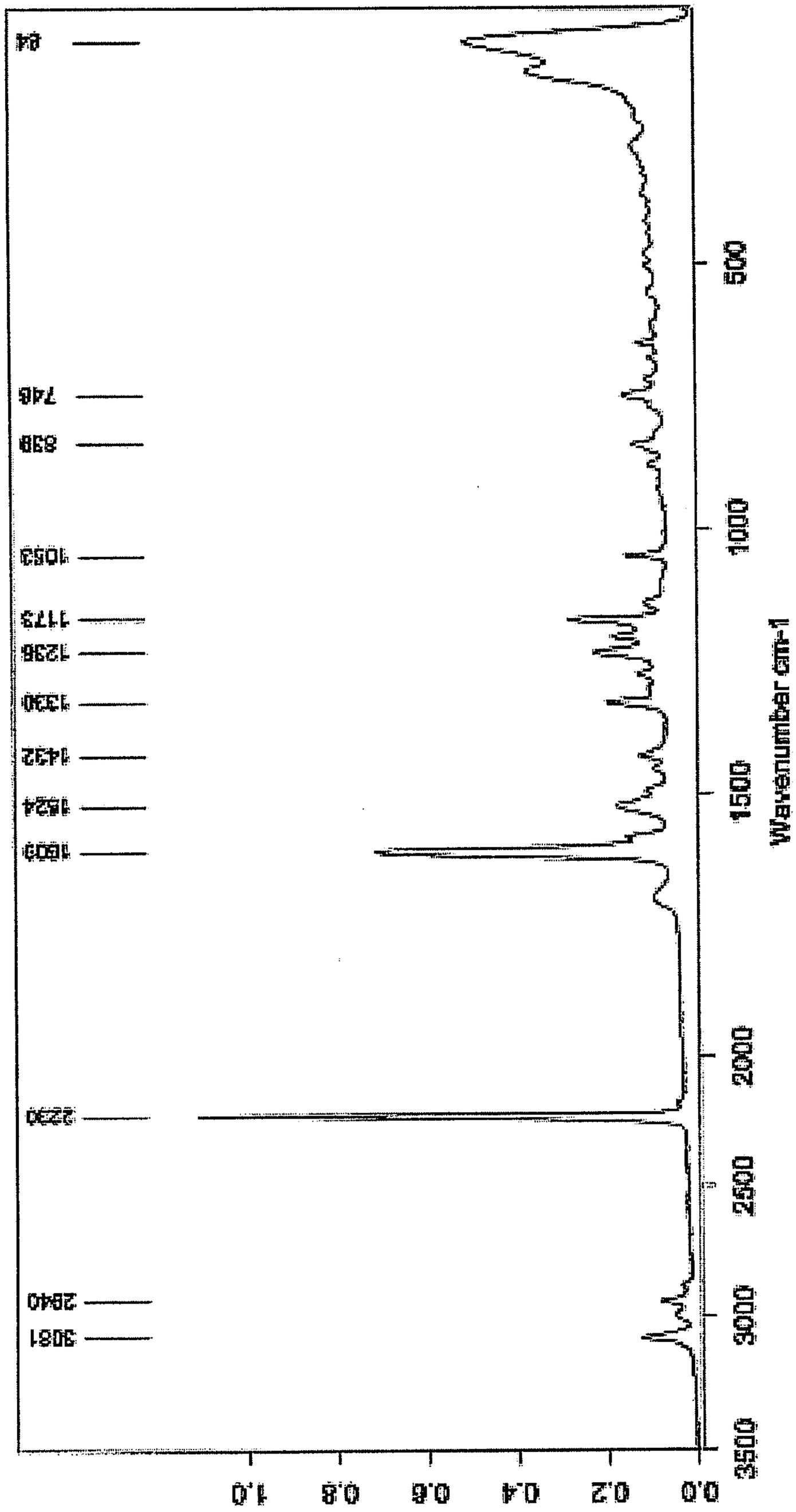

Wavenumber cm-1
500
1000
1500
2000
2500
3000
3500
0.0
0.2
0.4
0.6
0.8
1.0
2940
3061
2230
1530
1432
1324
1603
1053
1173
1236
746
839

FIGURE 5D

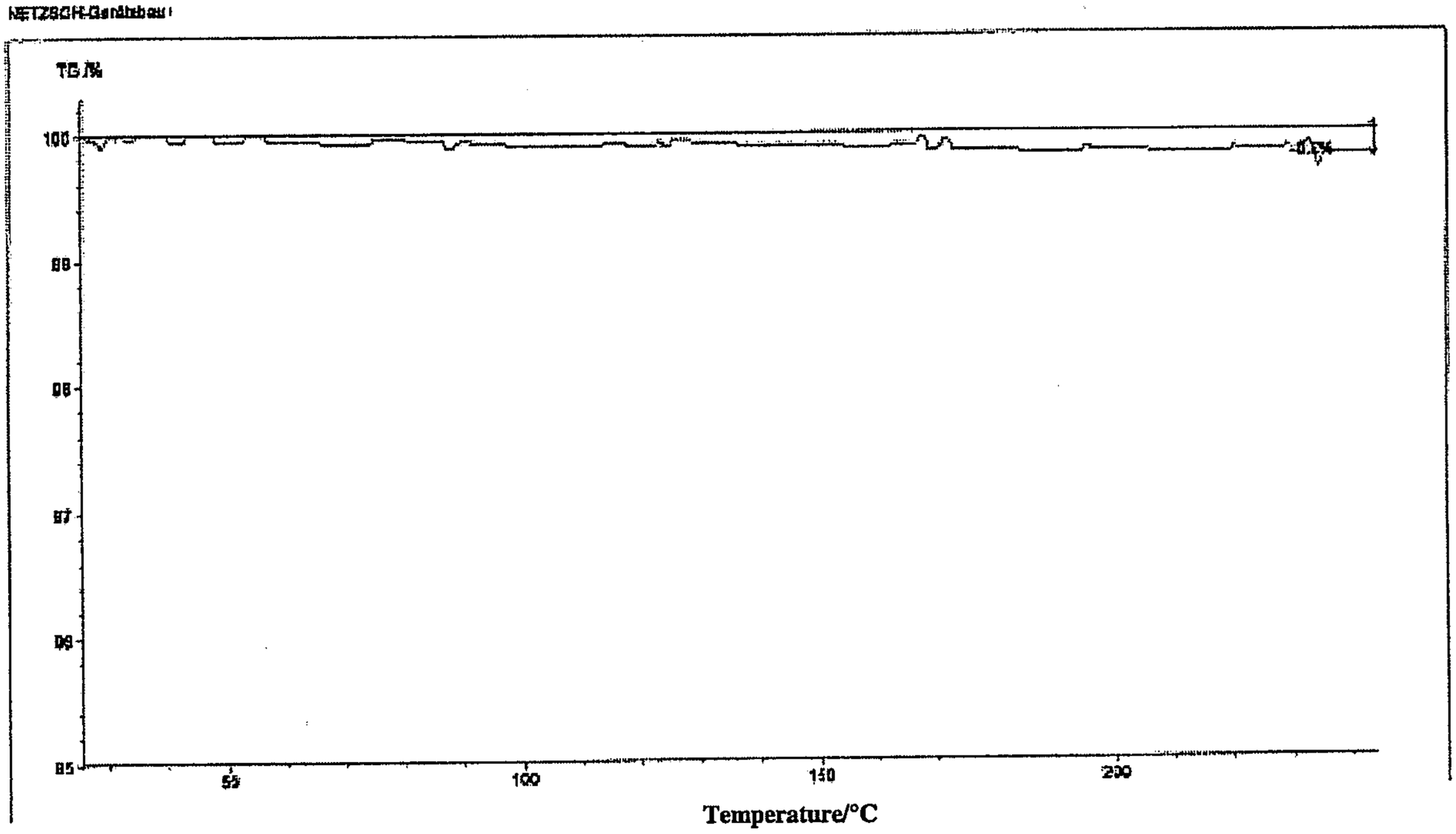


FIGURE 6A

FIGURE 6 B

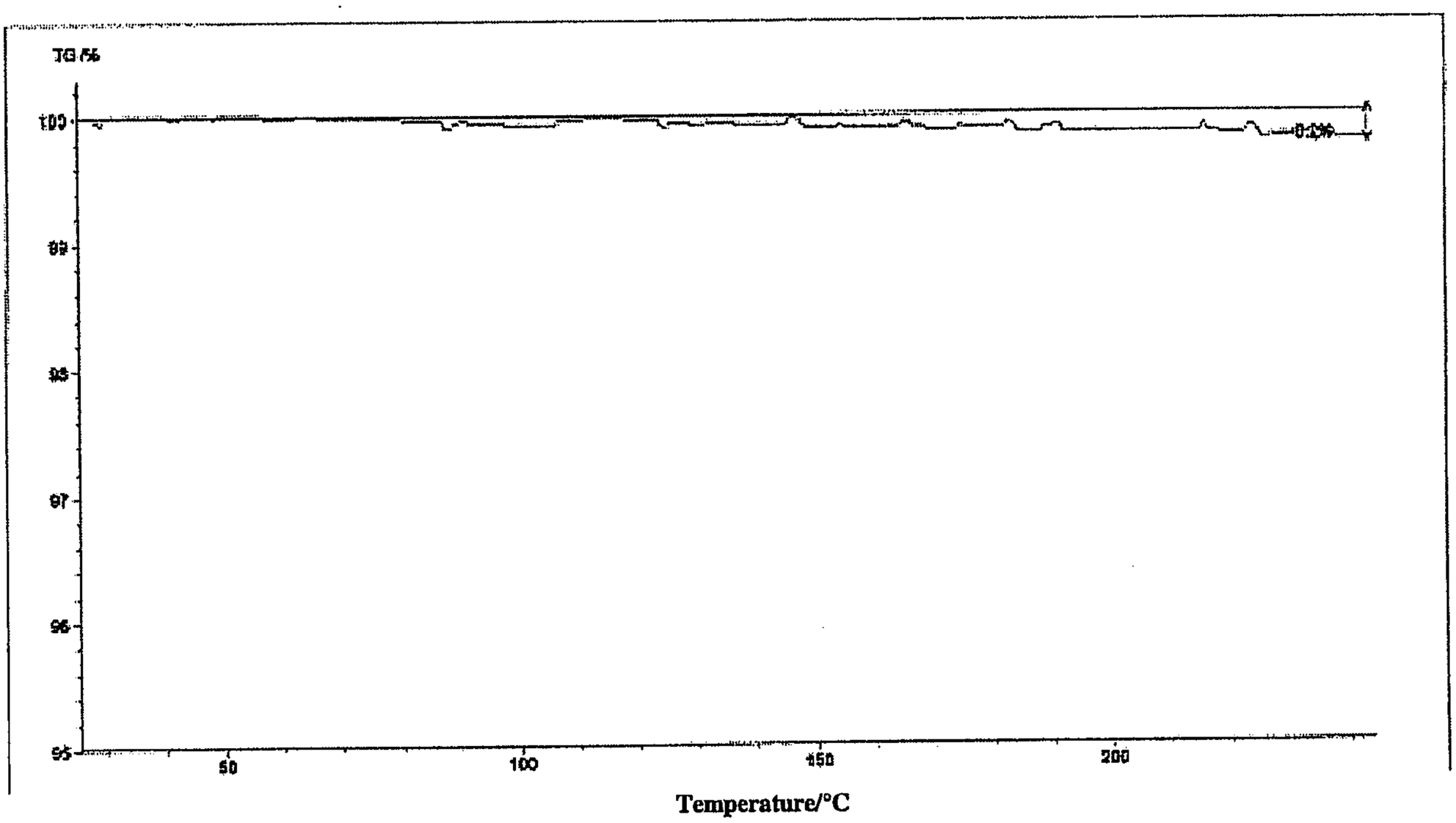


FIGURE 6C

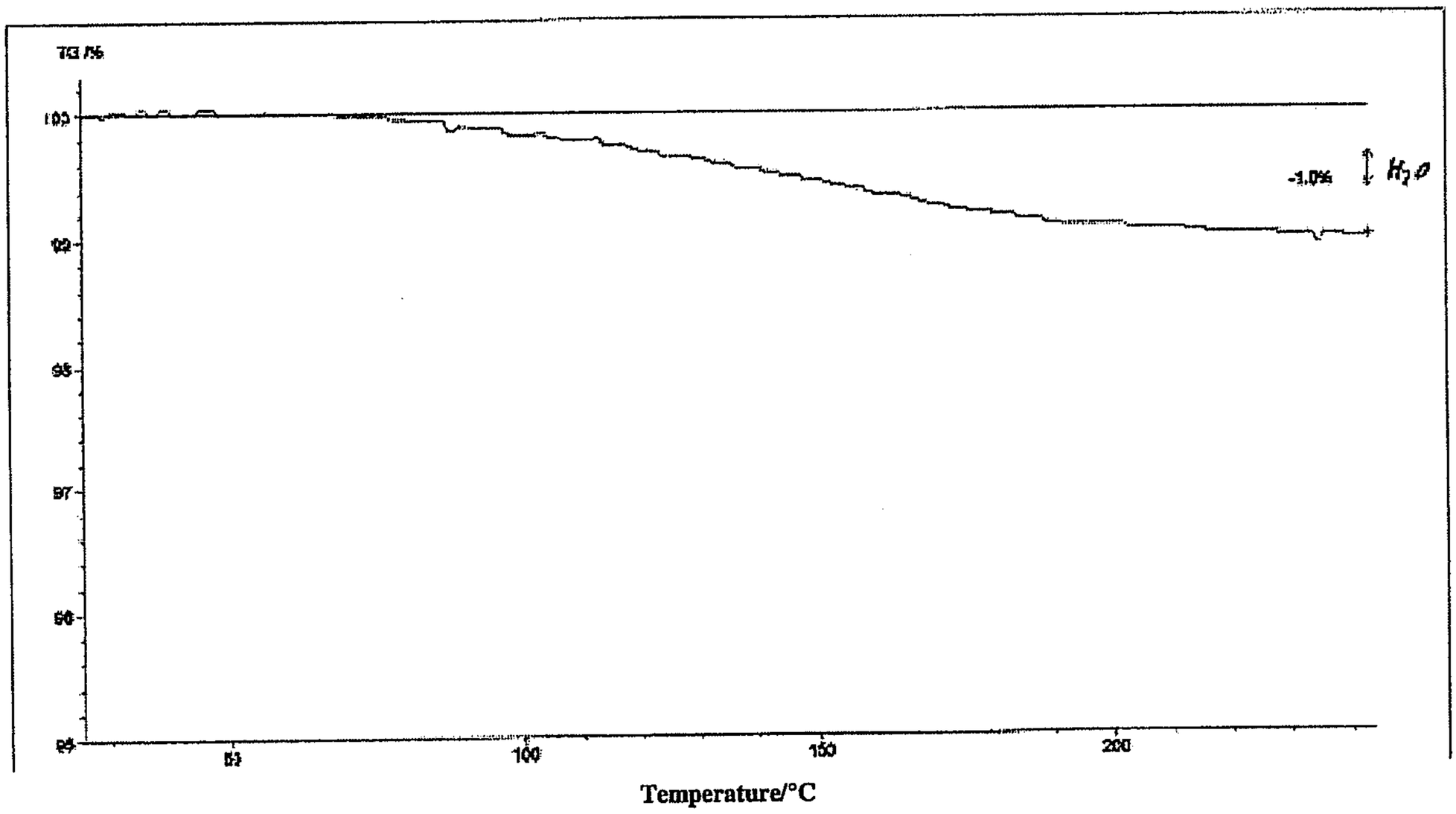


FIGURE 6D

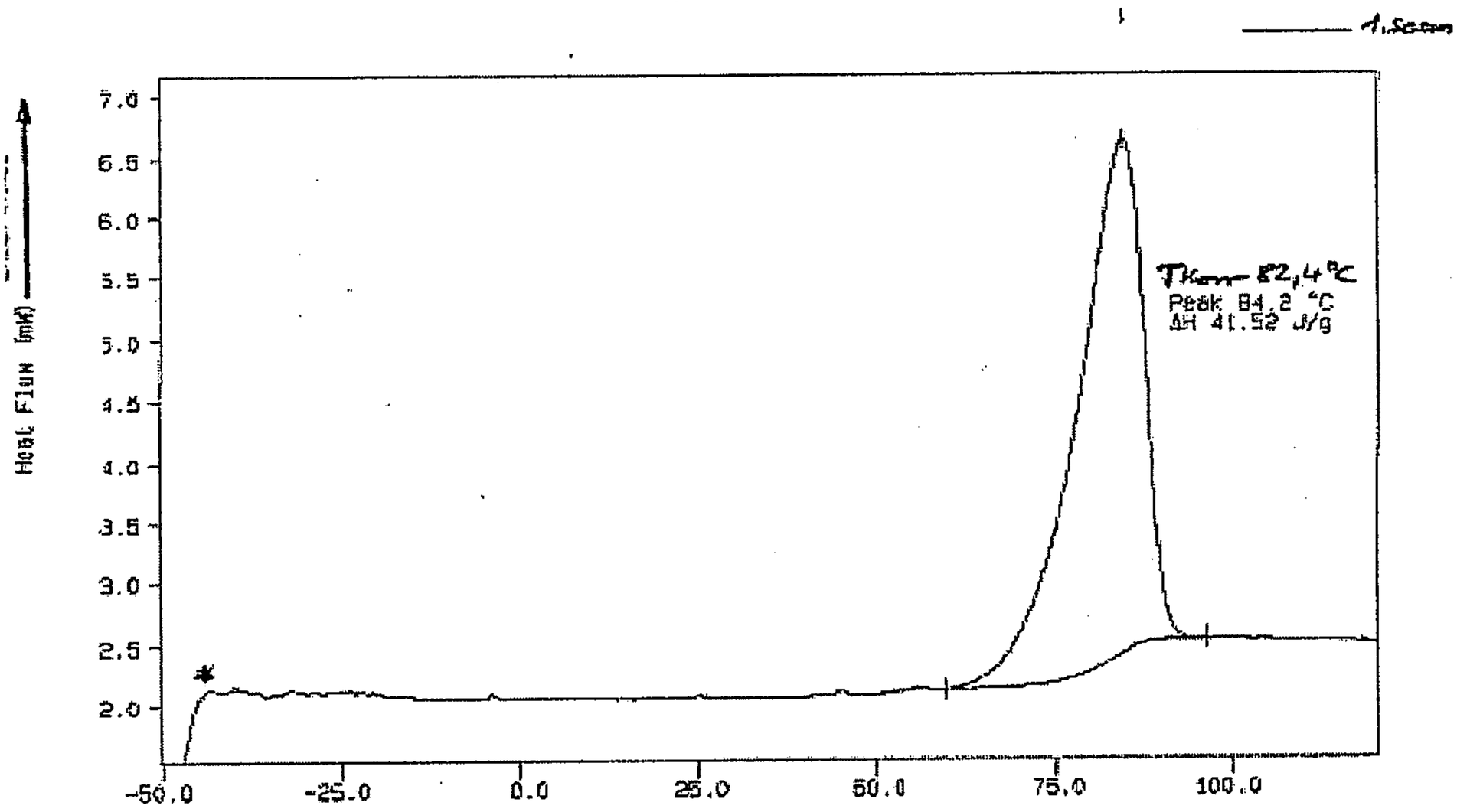


FIGURE 7A

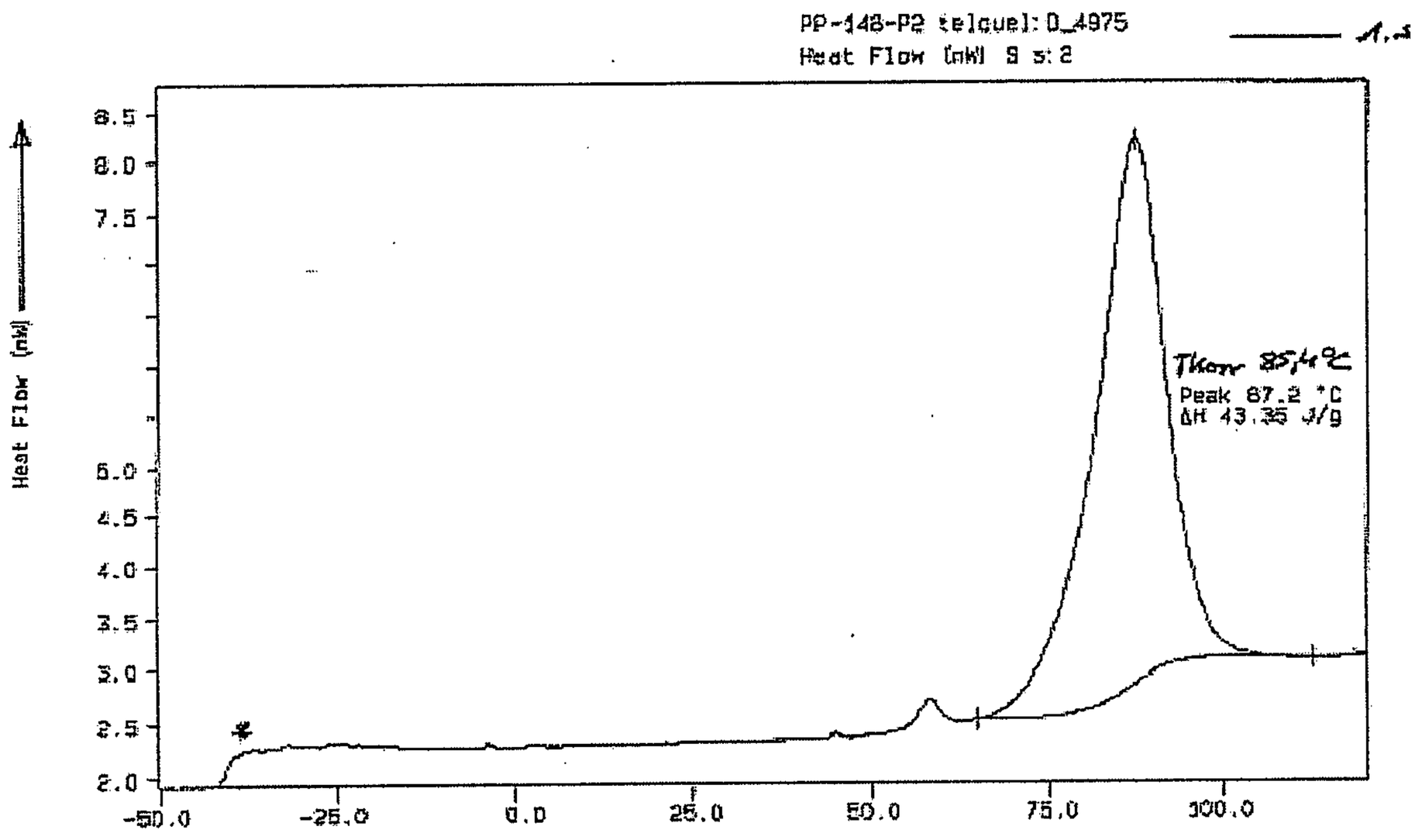


FIGURE 7B

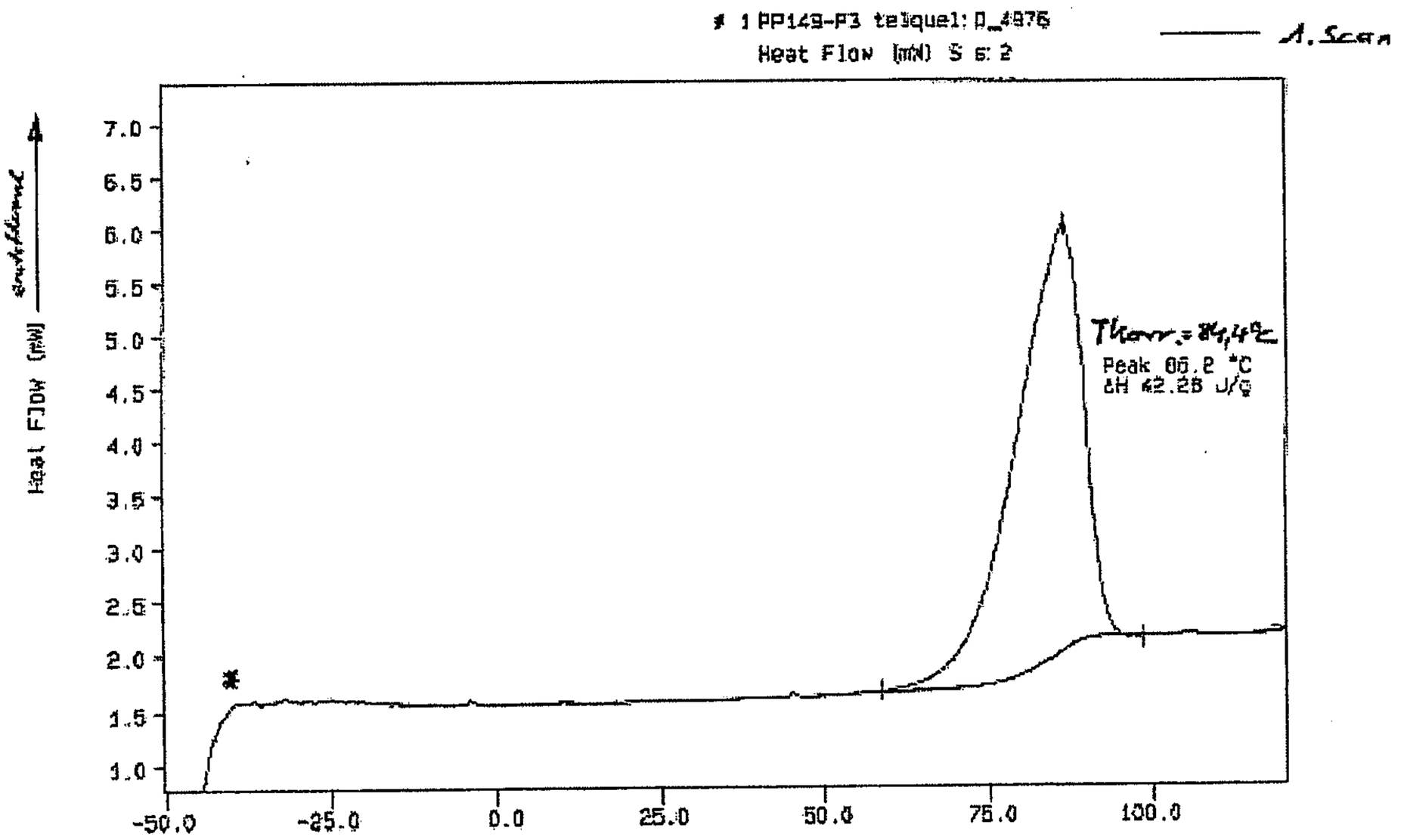


FIGURE 7C

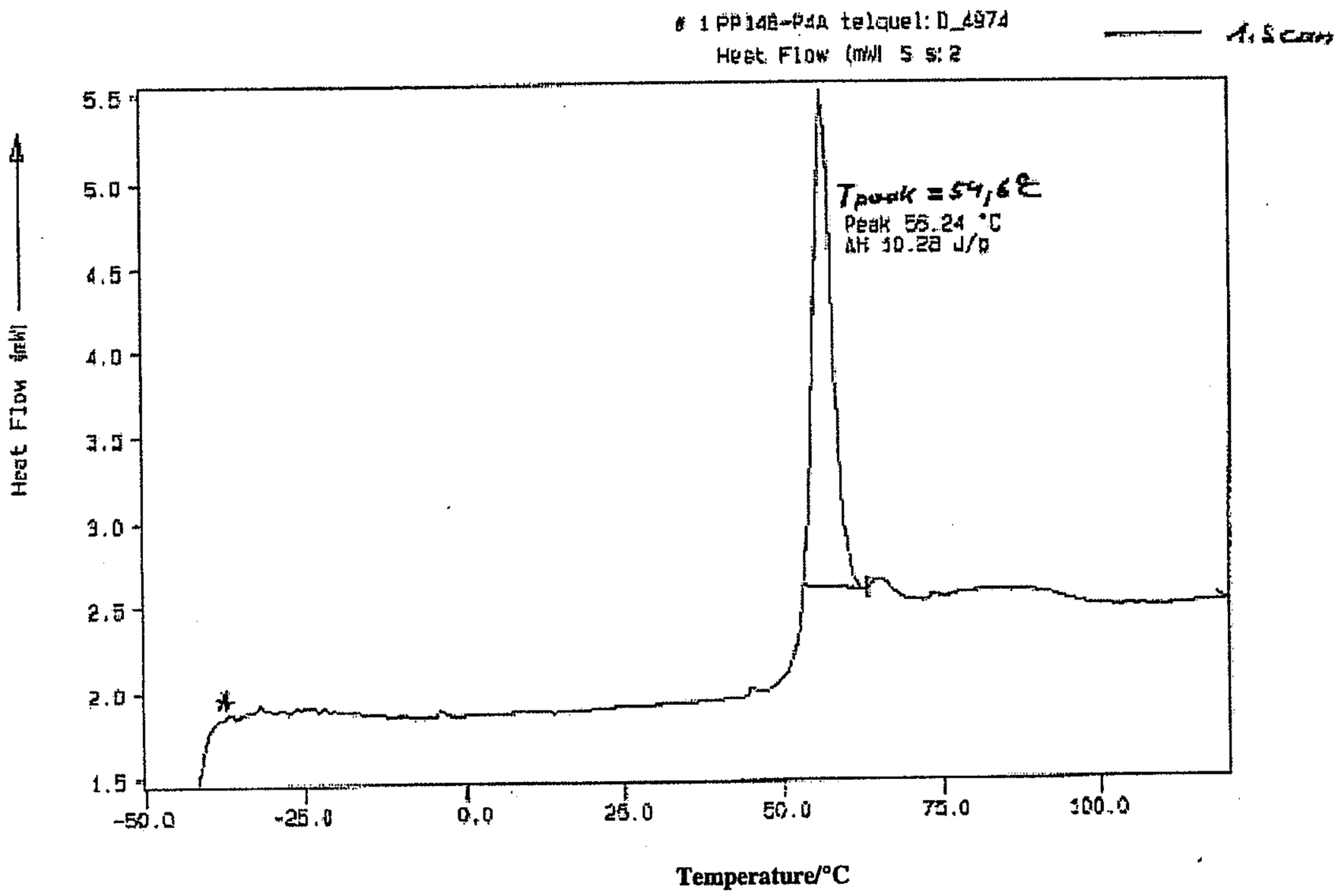
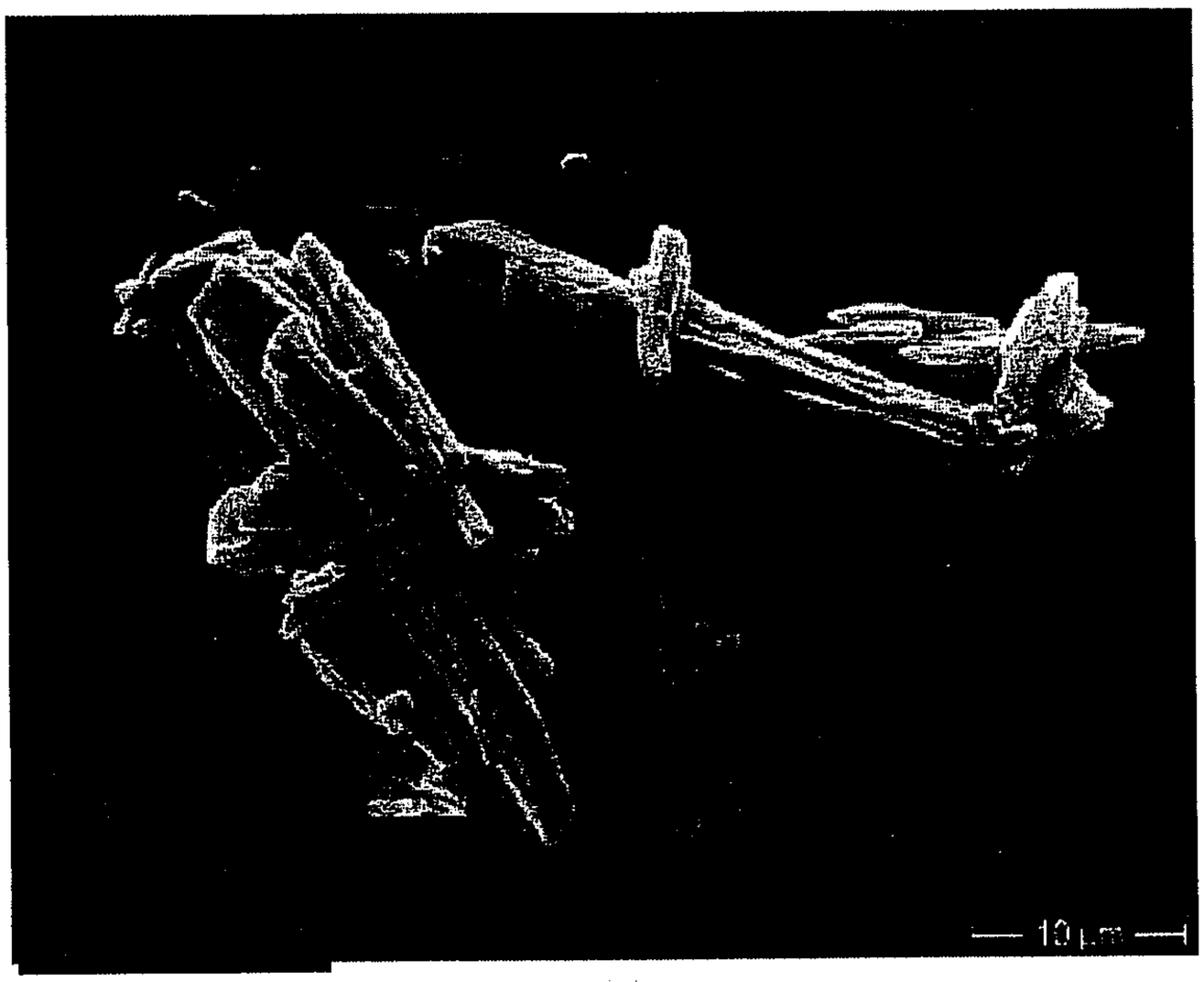


FIGURE 7D



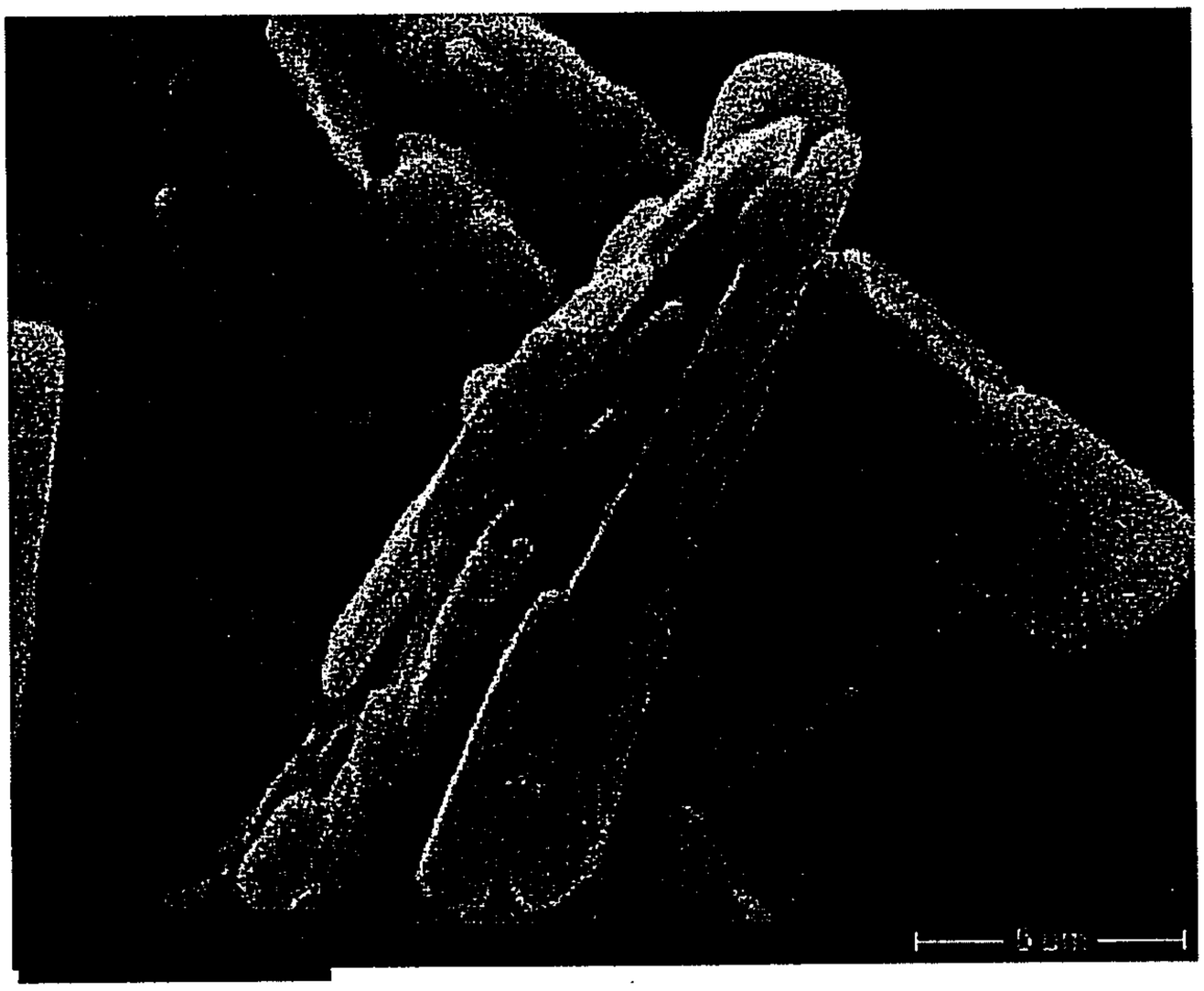


FIGURE 8A

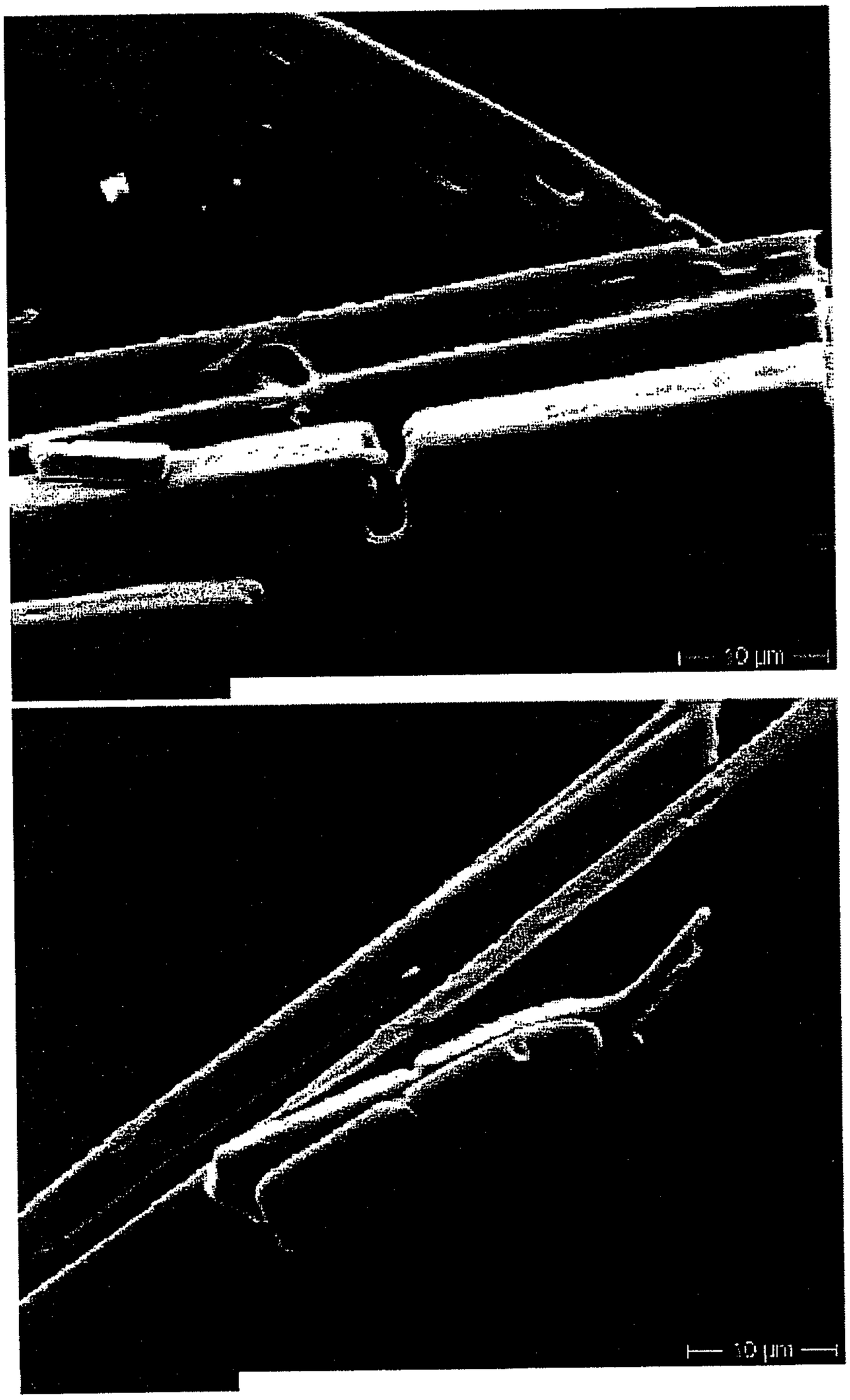


FIGURE 8B

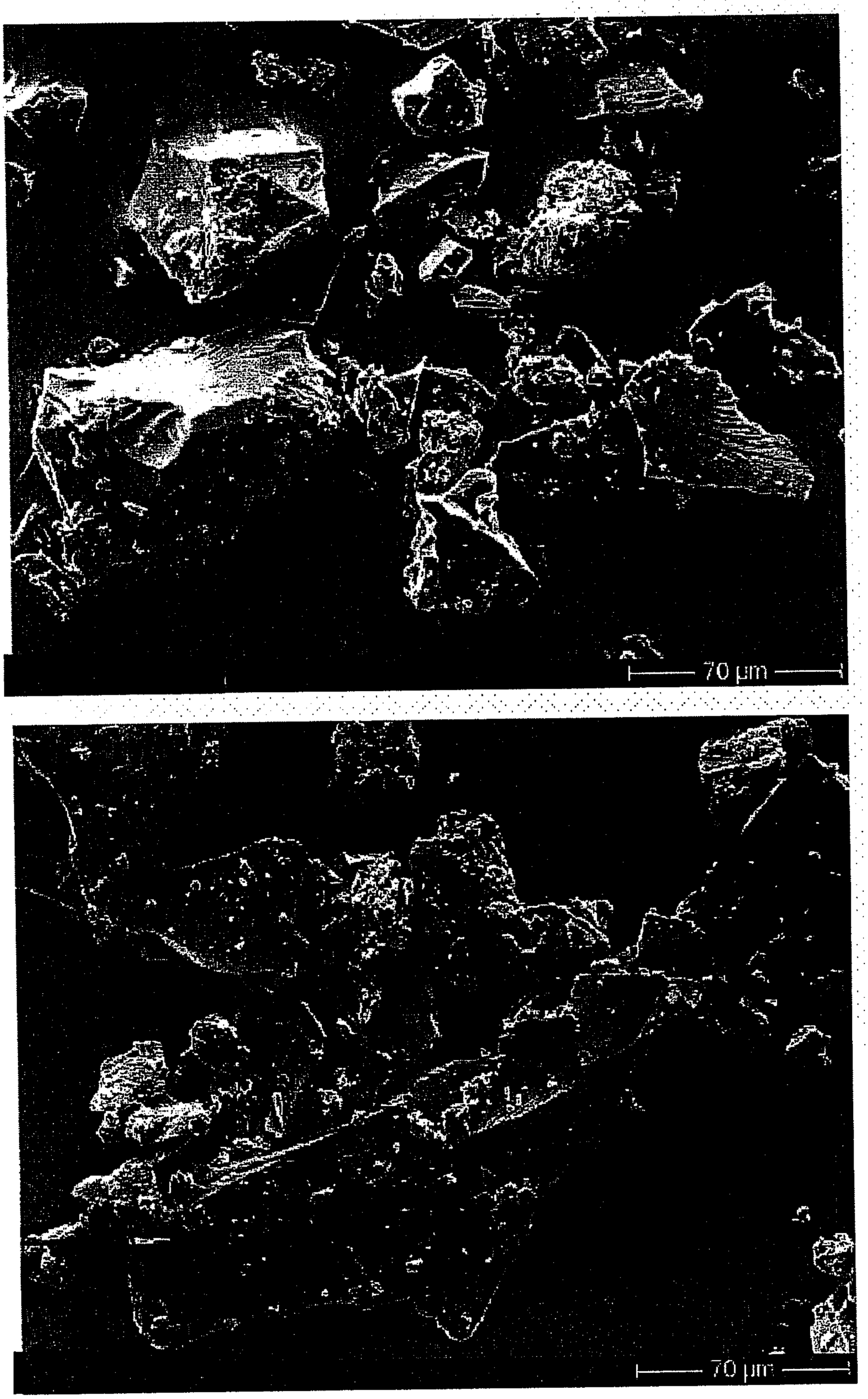


FIGURE 8C

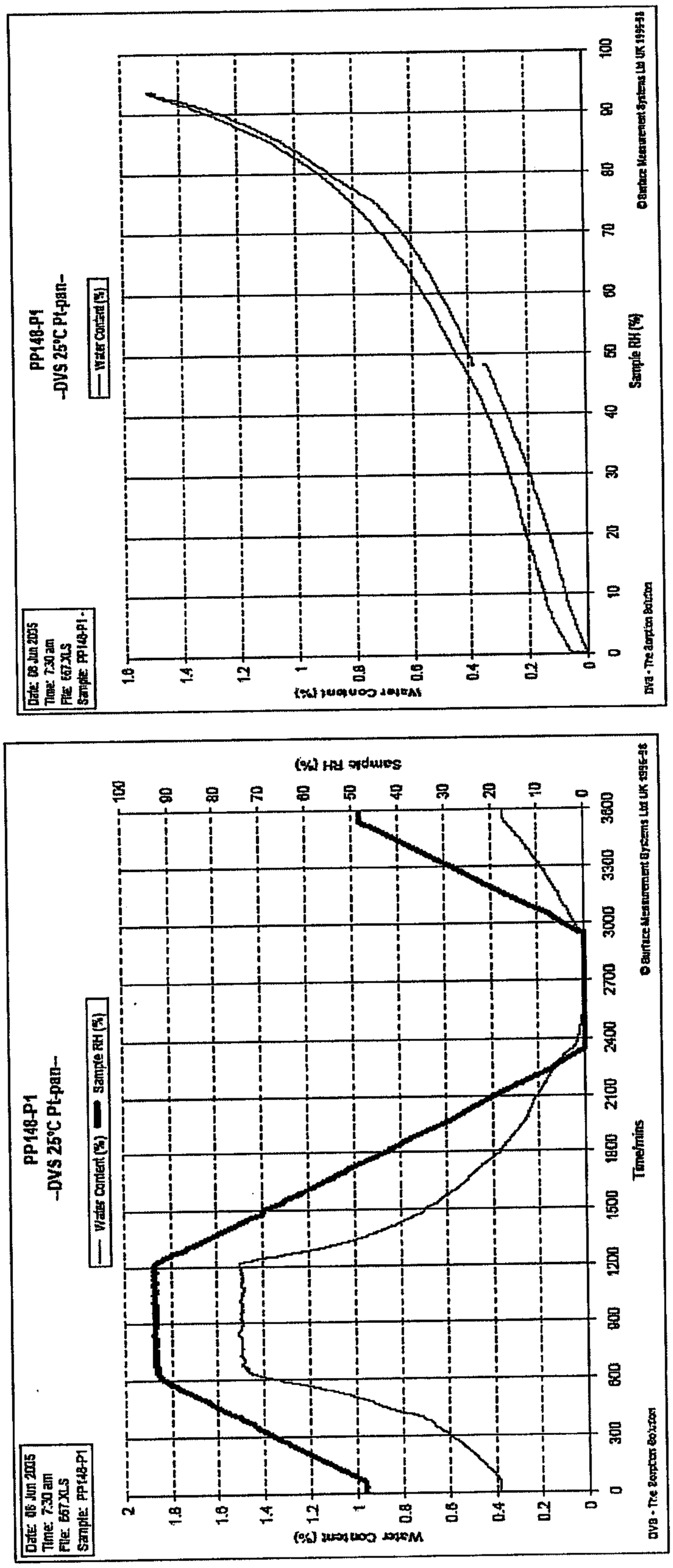
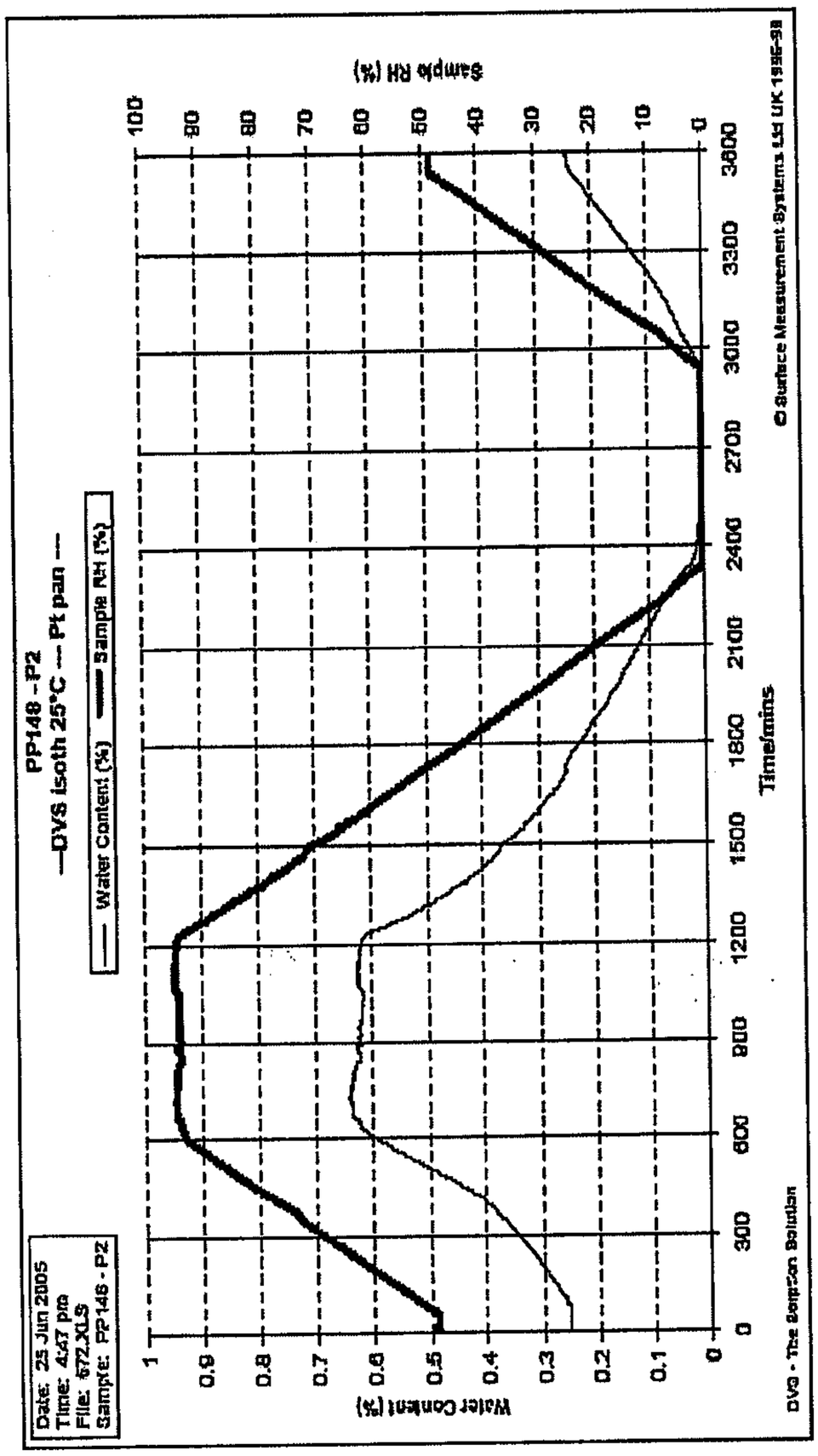

PP148-P1
-DVS 25°C Pt-pan-
Water Content (%)
Sample RH (%)
Date: 06 Jun 2005
Time: 7:30 am
File: 667.XLS
Sample: PP148-P1 -
Water Content (%)
Sample RH (%)
Time/mins
© Surface Measurement Systems Ltd UK 1995-98
DVS - The Adsorption Solution

FIGURE 9A

FIGURE 9B


PP148 - P2
--DVS isoth 25°C --- Pt pan ---
Water Content (%)
Sample RH (%)
Time/mins
Date: 25 Jun 2005
Time: 4:47 pm
File: 672.XLS
Sample: PP148 - P2
© Surface Measurement Systems Ltd UK 1996-98
DVS - The Sorption Solution

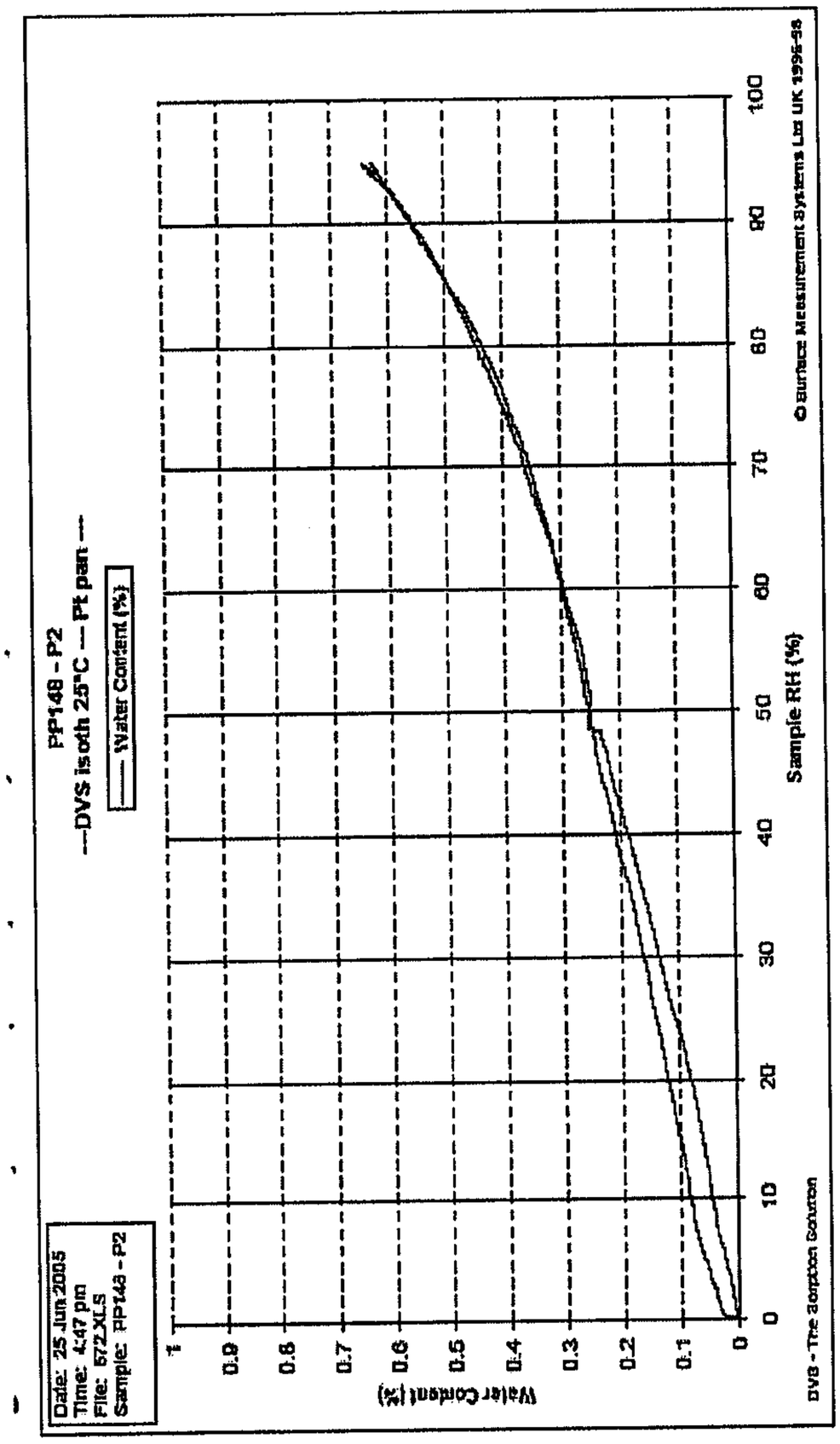
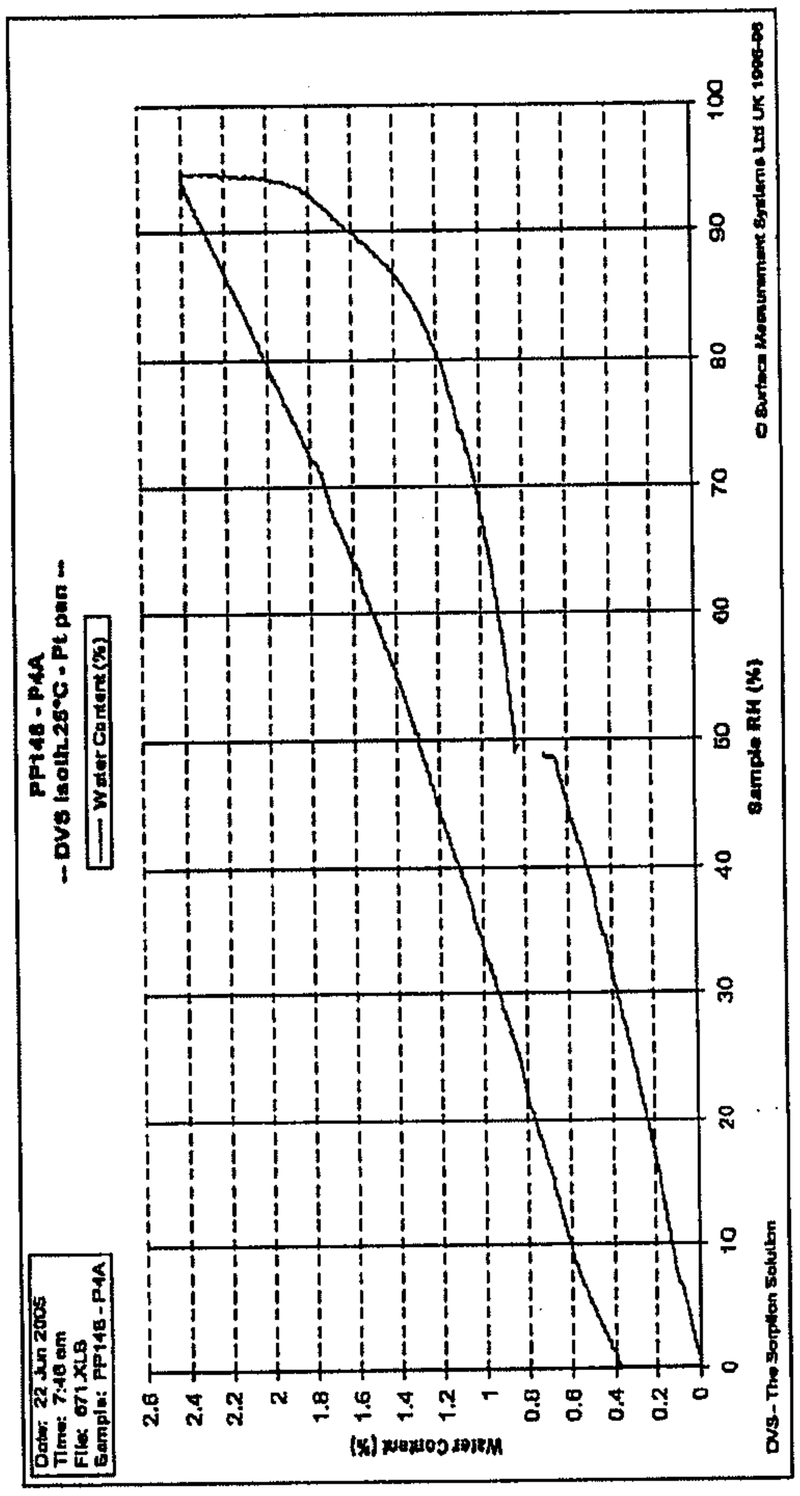
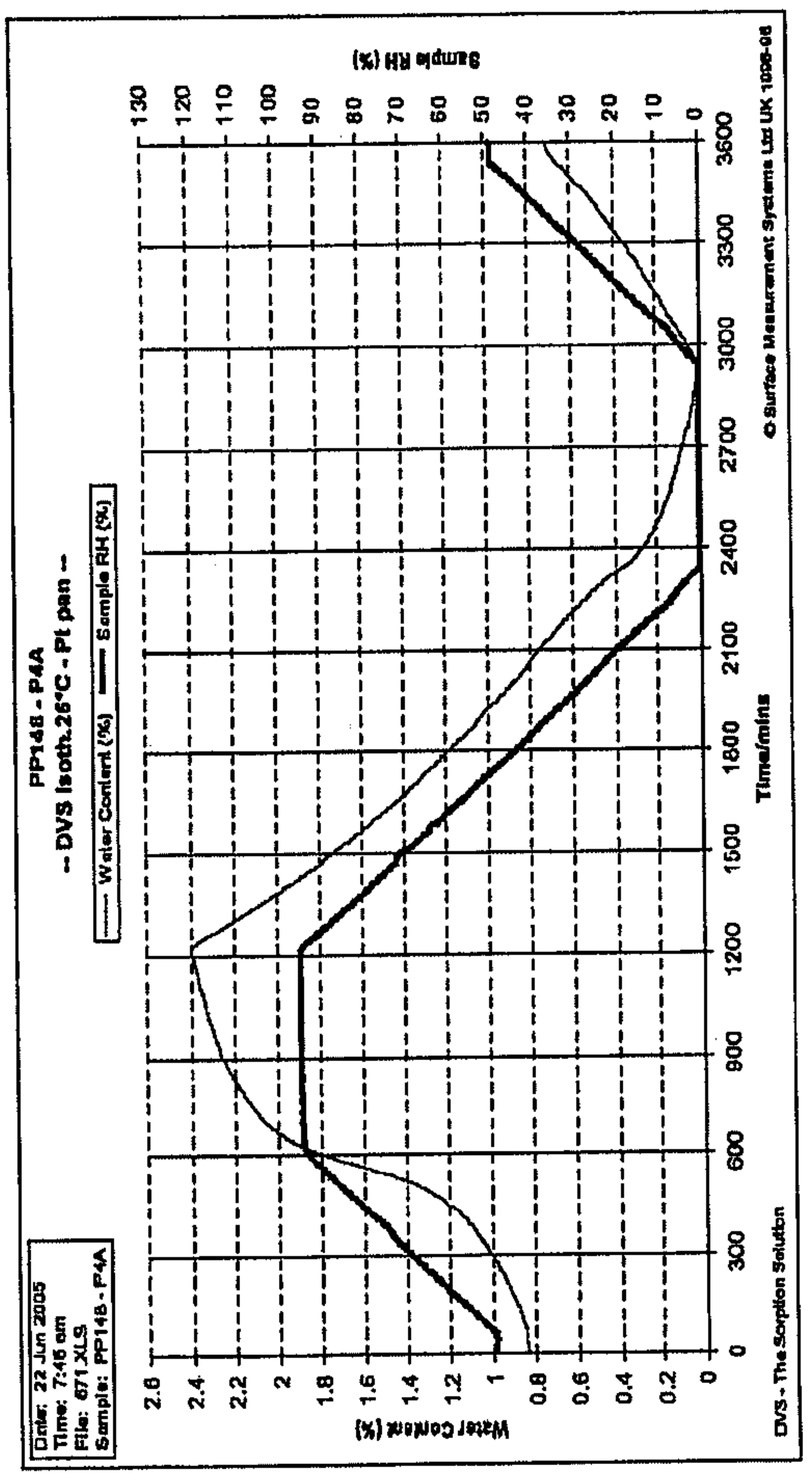

PP148 - P2
--DVS isoth 25°C --- Pt pan ---
Water Content (%)
Sample RH (%)
Date: 25 Jun 2005
Time: 4:47 pm
File: 672.XLS
Sample: PP148 - P2
© Surface Measurement Systems Ltd UK 1996-98
DVS - The Sorption Solution

FIGURE 9C


PP148 - P4A
-- DVS Isoth.25°C - Pt pan --
Water Content (%)
Sample RH (%)
Date: 22 Jun 2005
Time: 7:46 am
File: 671.XLS
Sample: PP148 - P4A
© Surface Measurement Systems Ltd UK 1998-05
DVS - The Sorption Solution


PP148 - P4A
-- DVS Isoth.25°C - Pt pan --
Water Content (%)
Sample RH (%)
Time/mins
Date: 22 Jun 2005
Time: 7:46 am
File: 671.XLS
Sample: PP148 - P4A
© Surface Measurement Systems Ltd UK 1998-05
DVS - The Sorption Solution

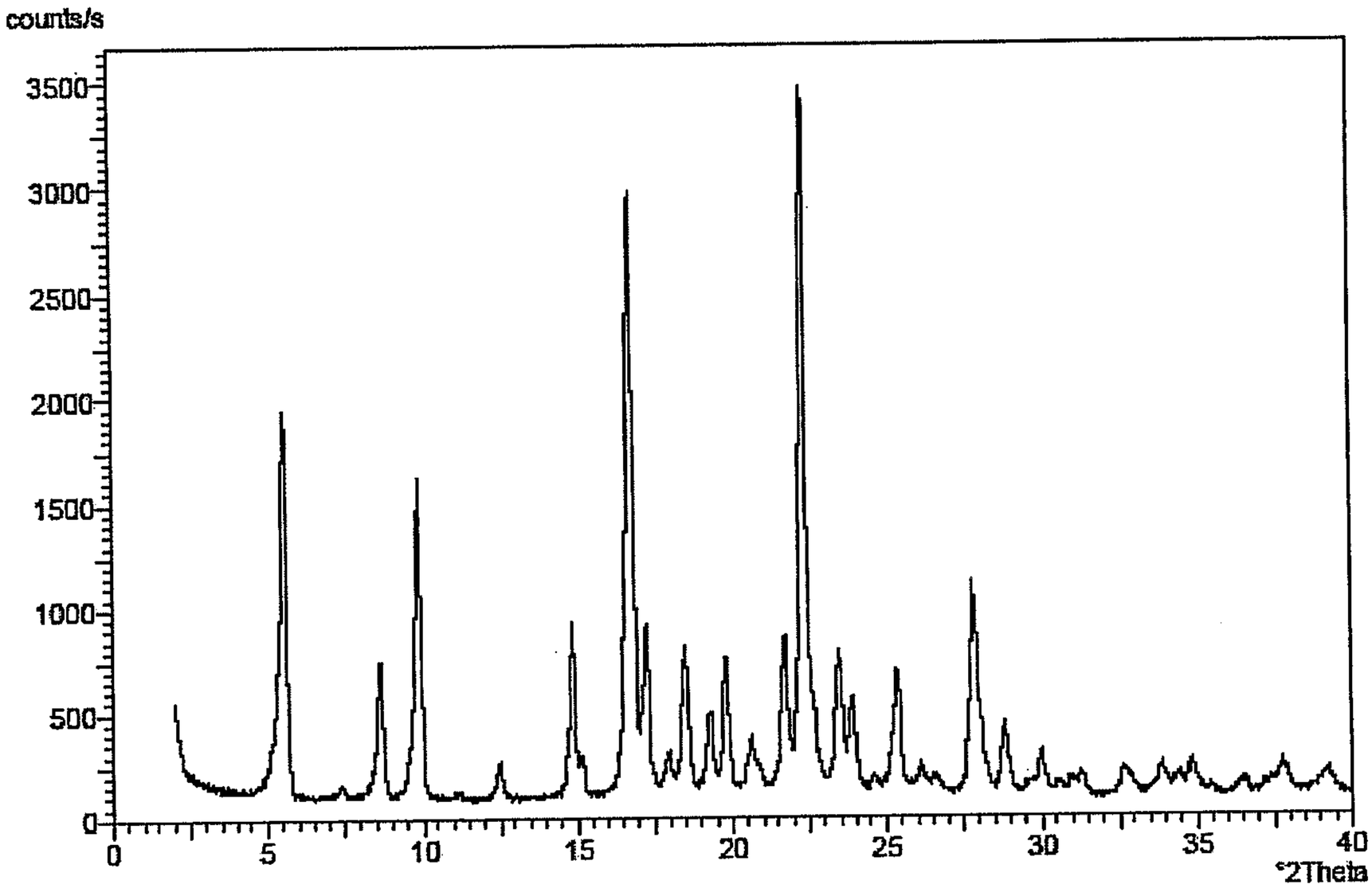


FIGURE 10A

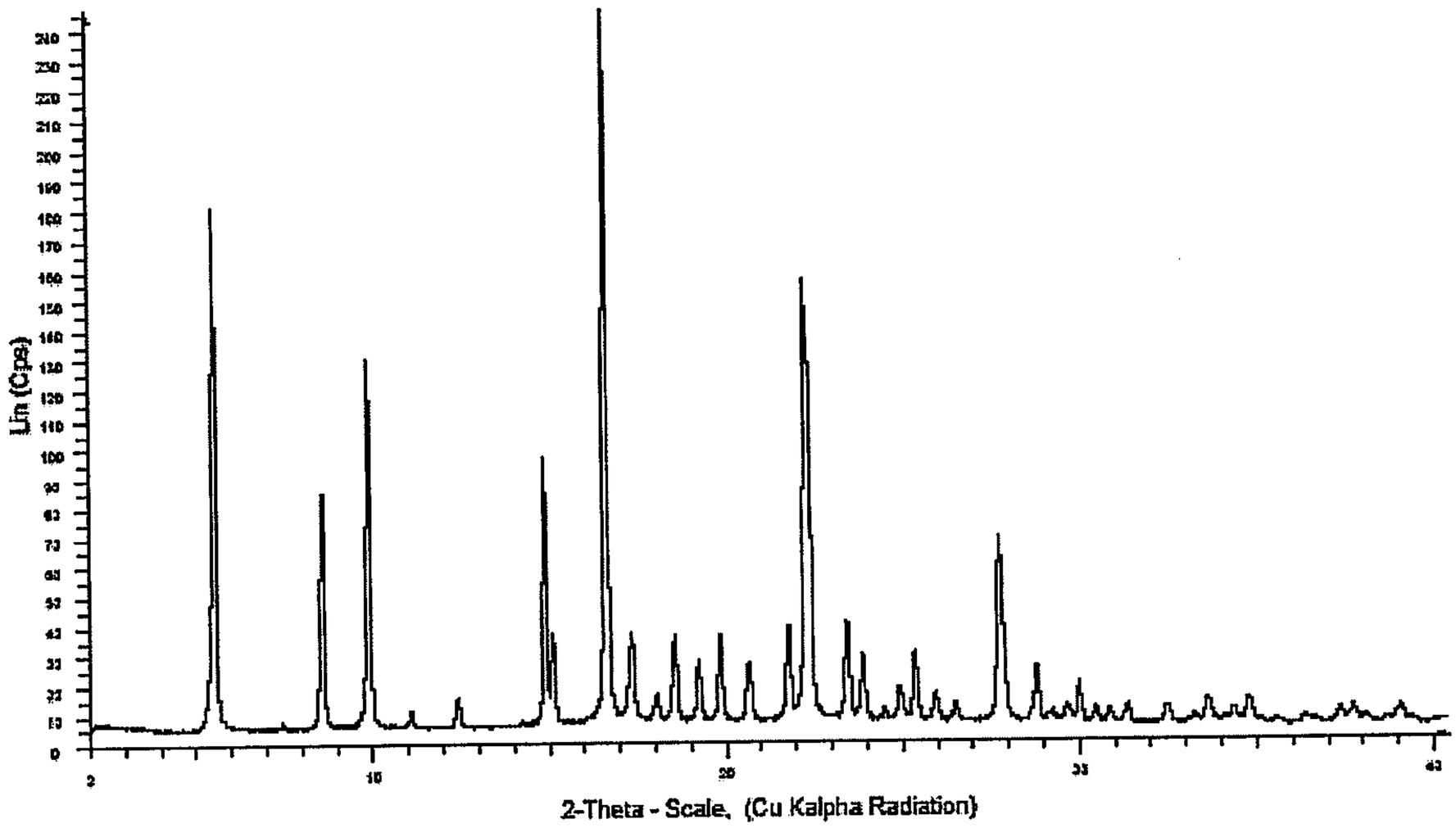


FIGURE 10B

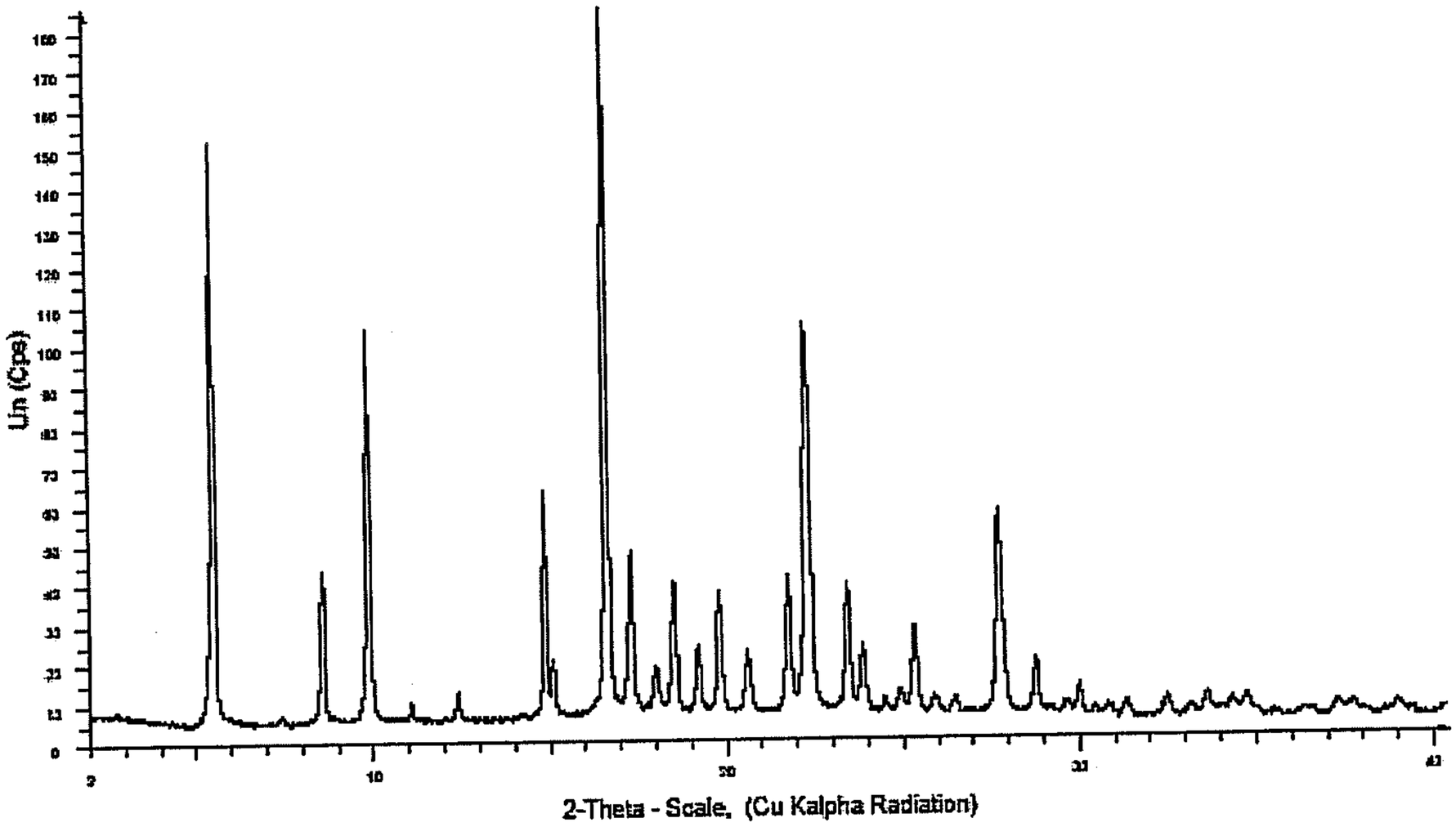


FIGURE 10C

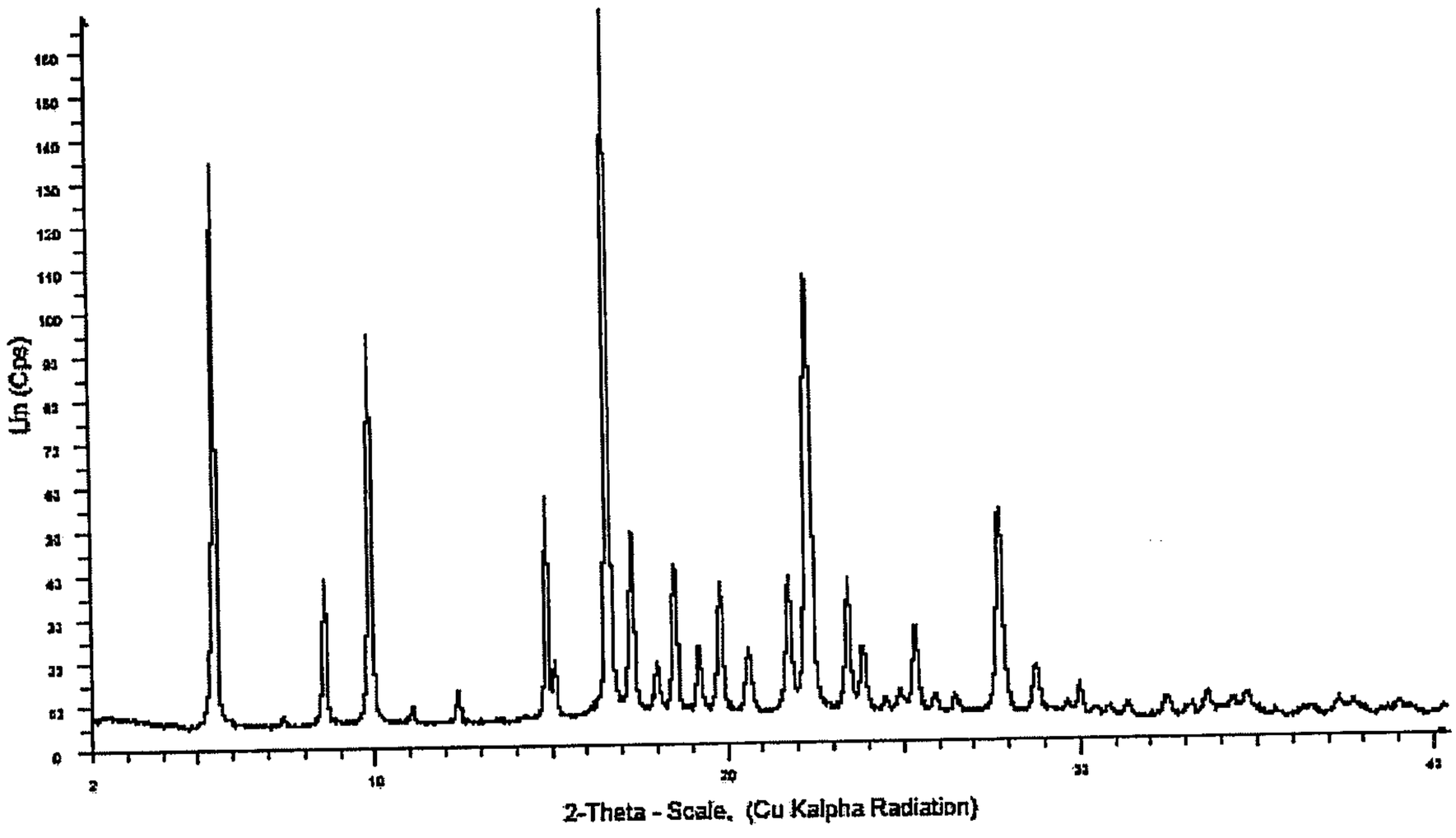


FIGURE 10D

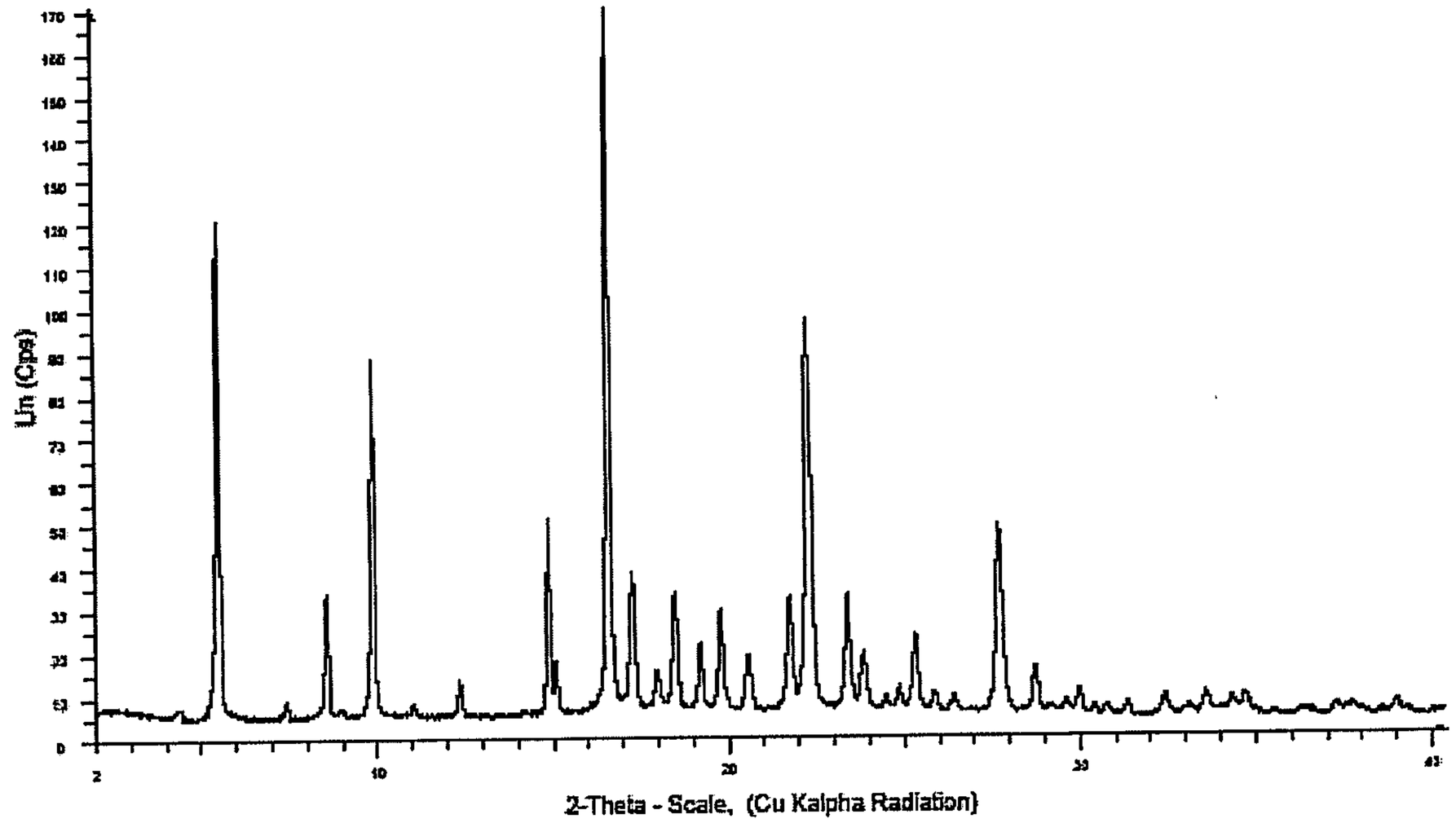


FIGURE 10E

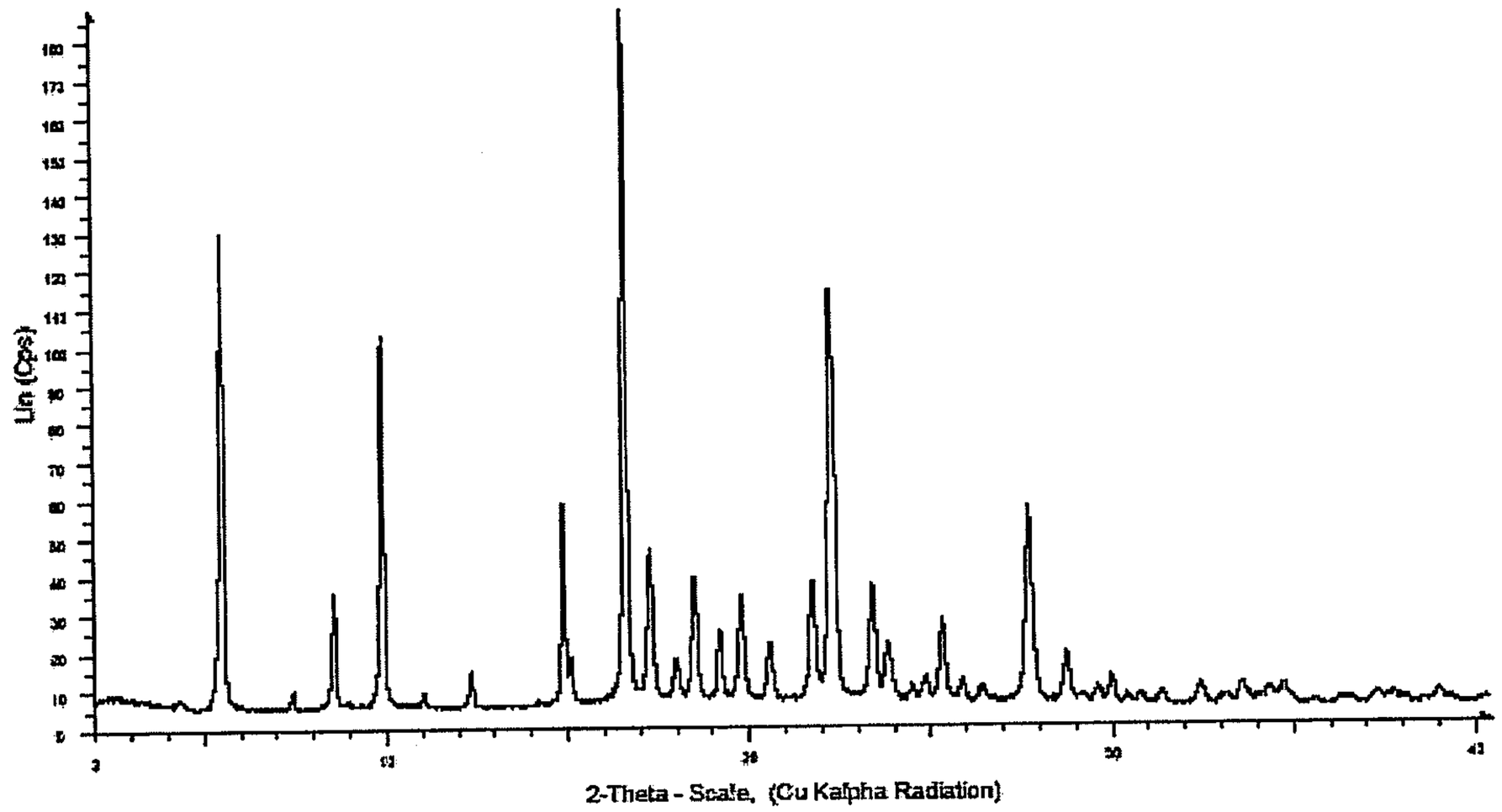


FIGURE 10F

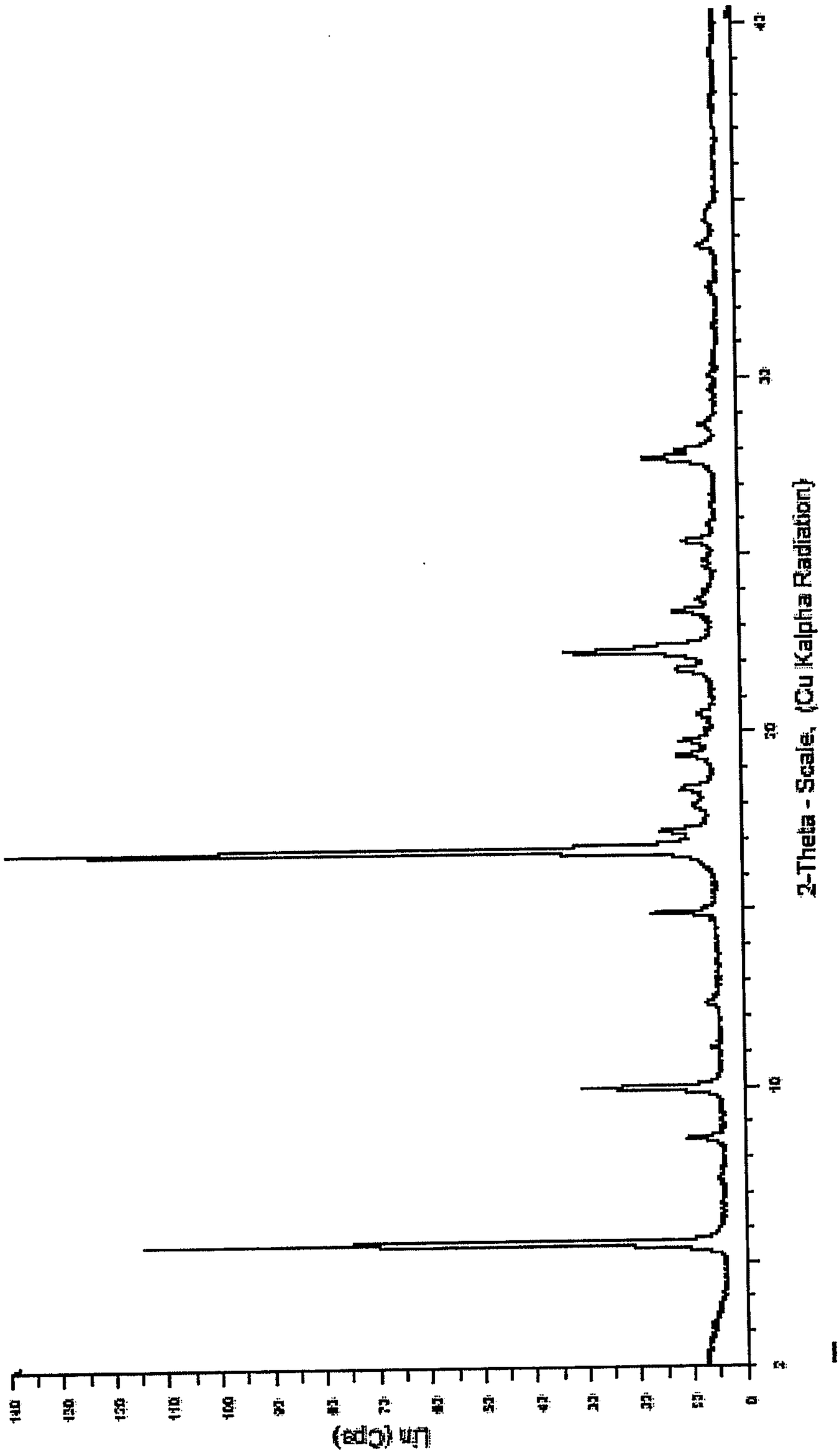


FIGURE 11A

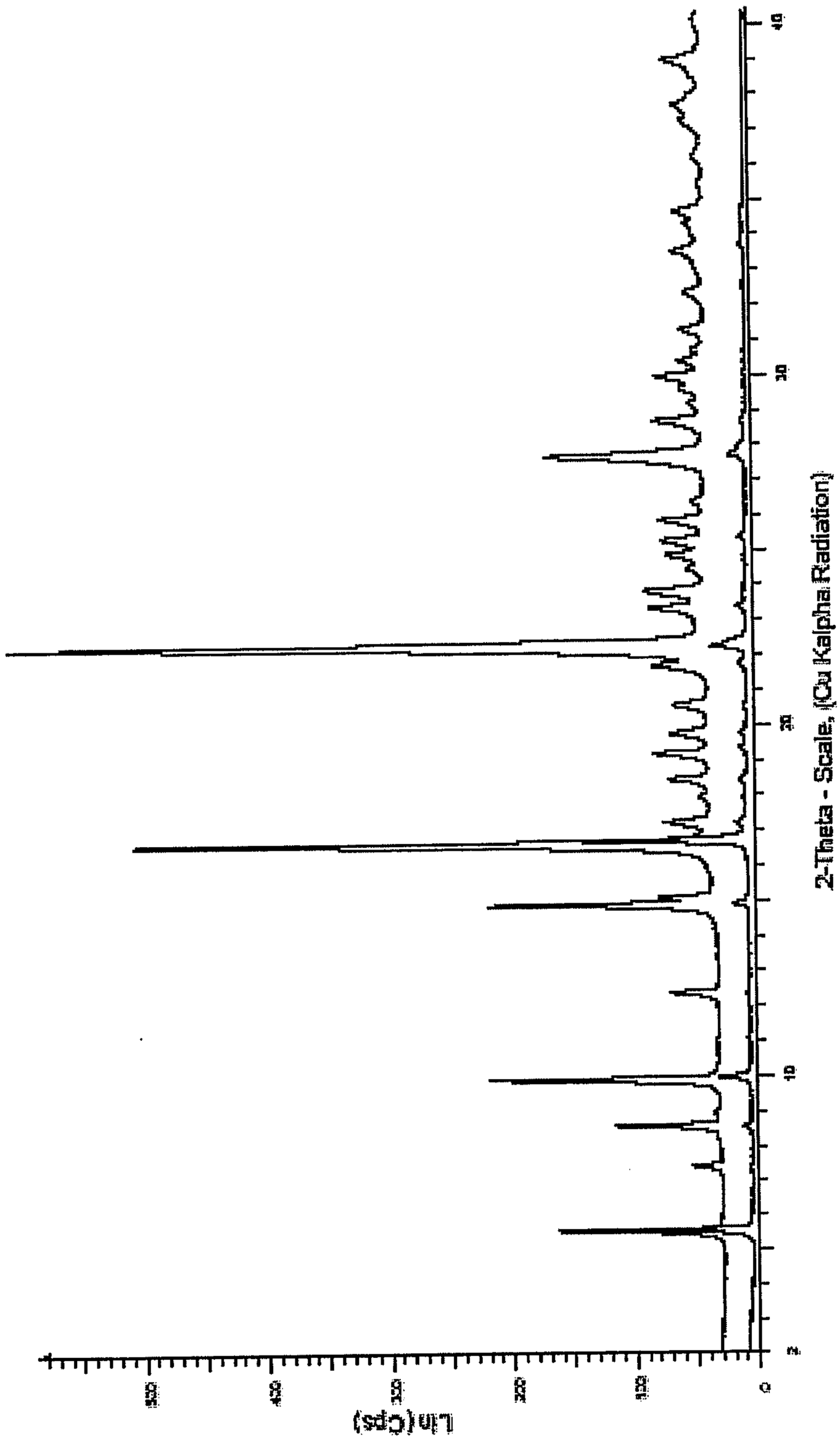


FIGURE 11B

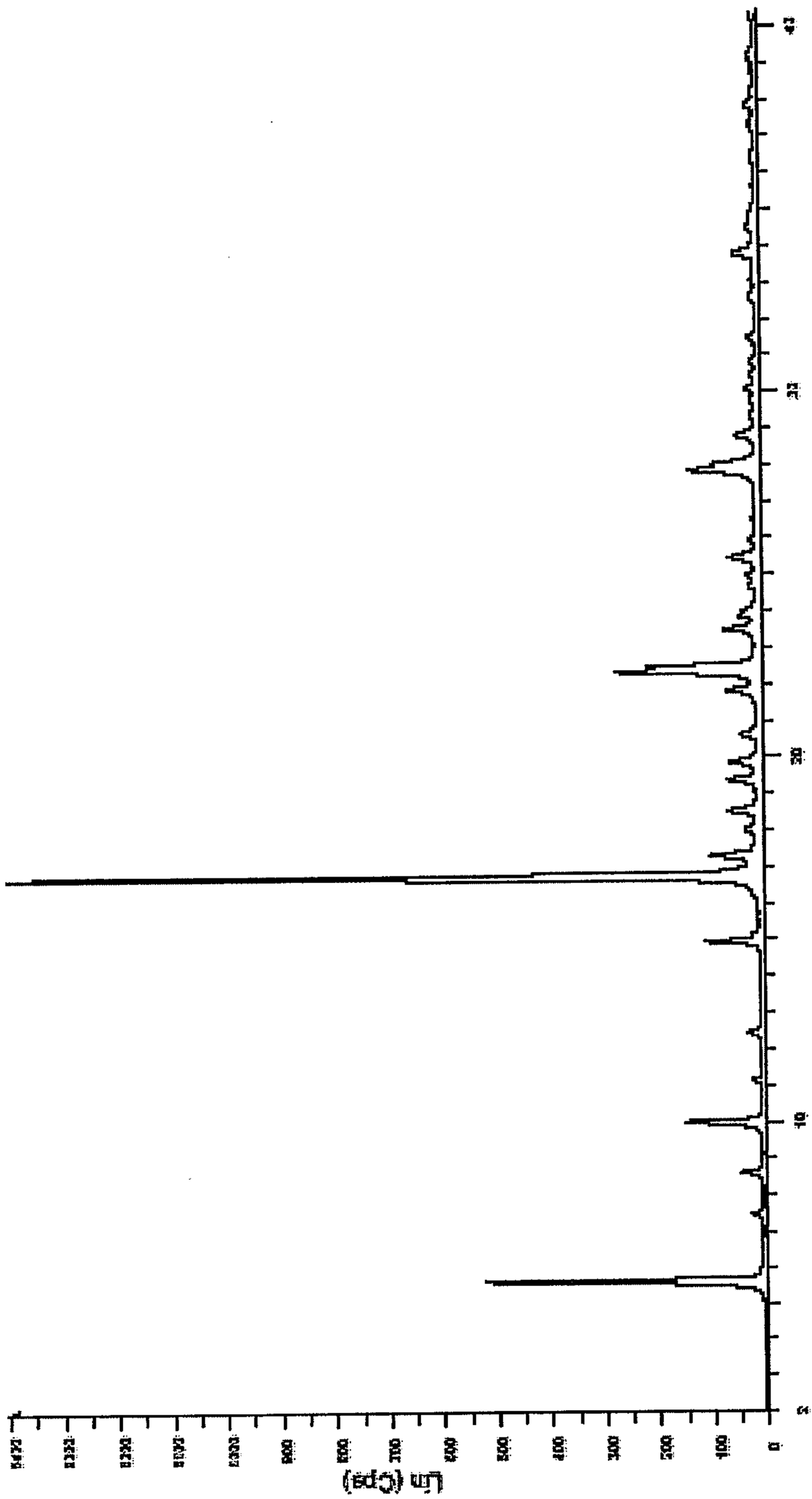


FIGURE 11C

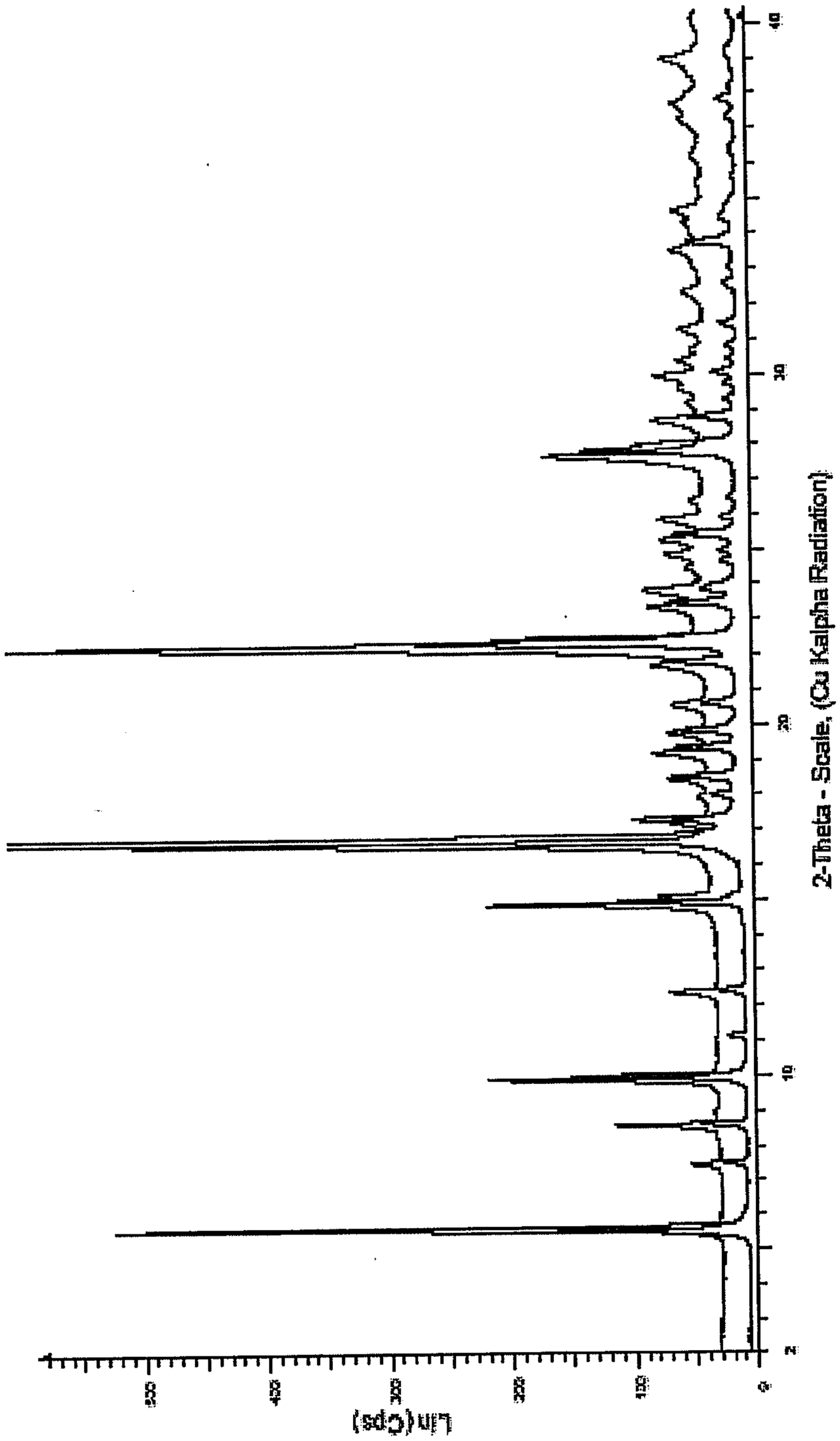


FIGURE 11D

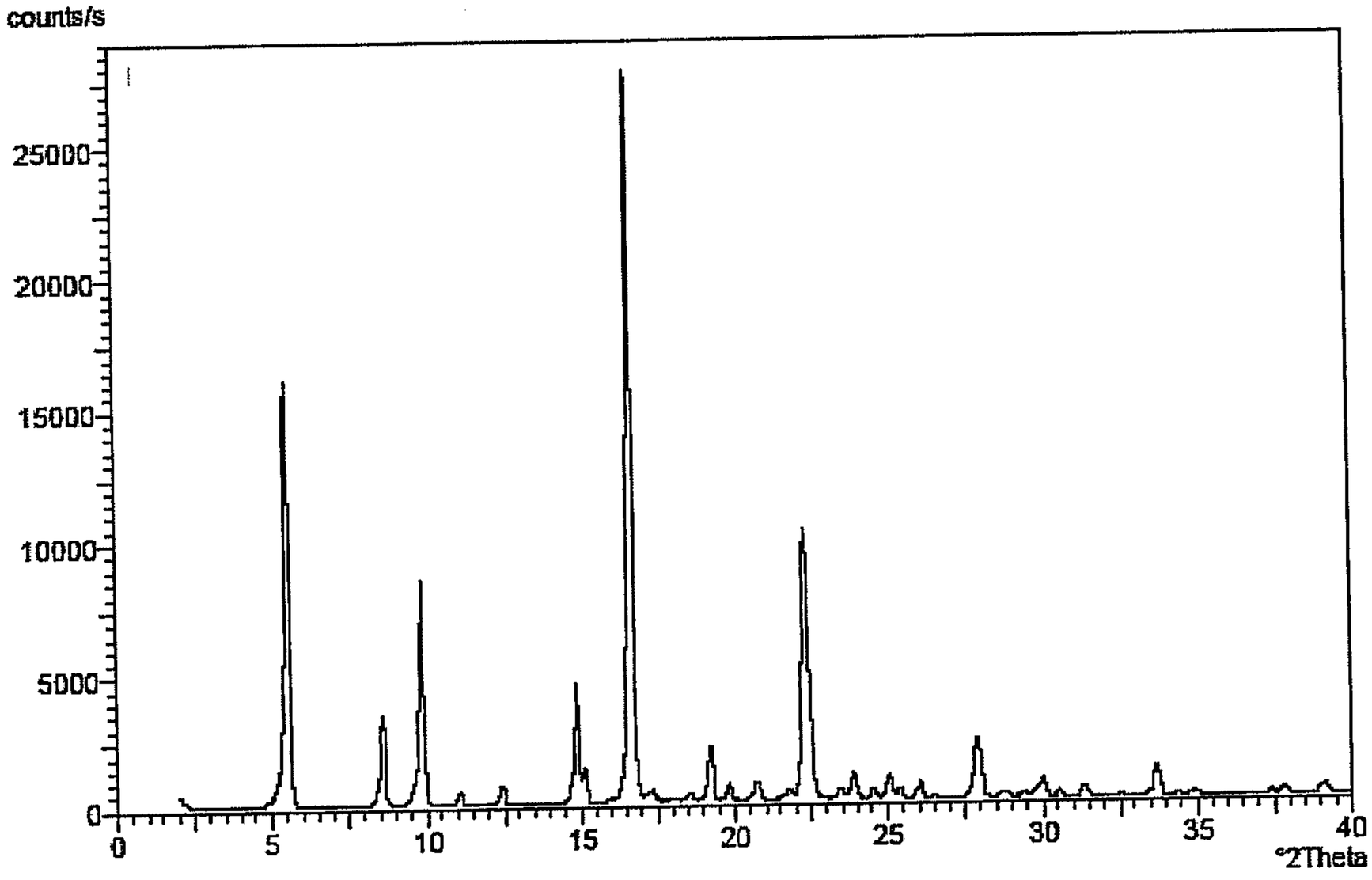


FIGURE 12A

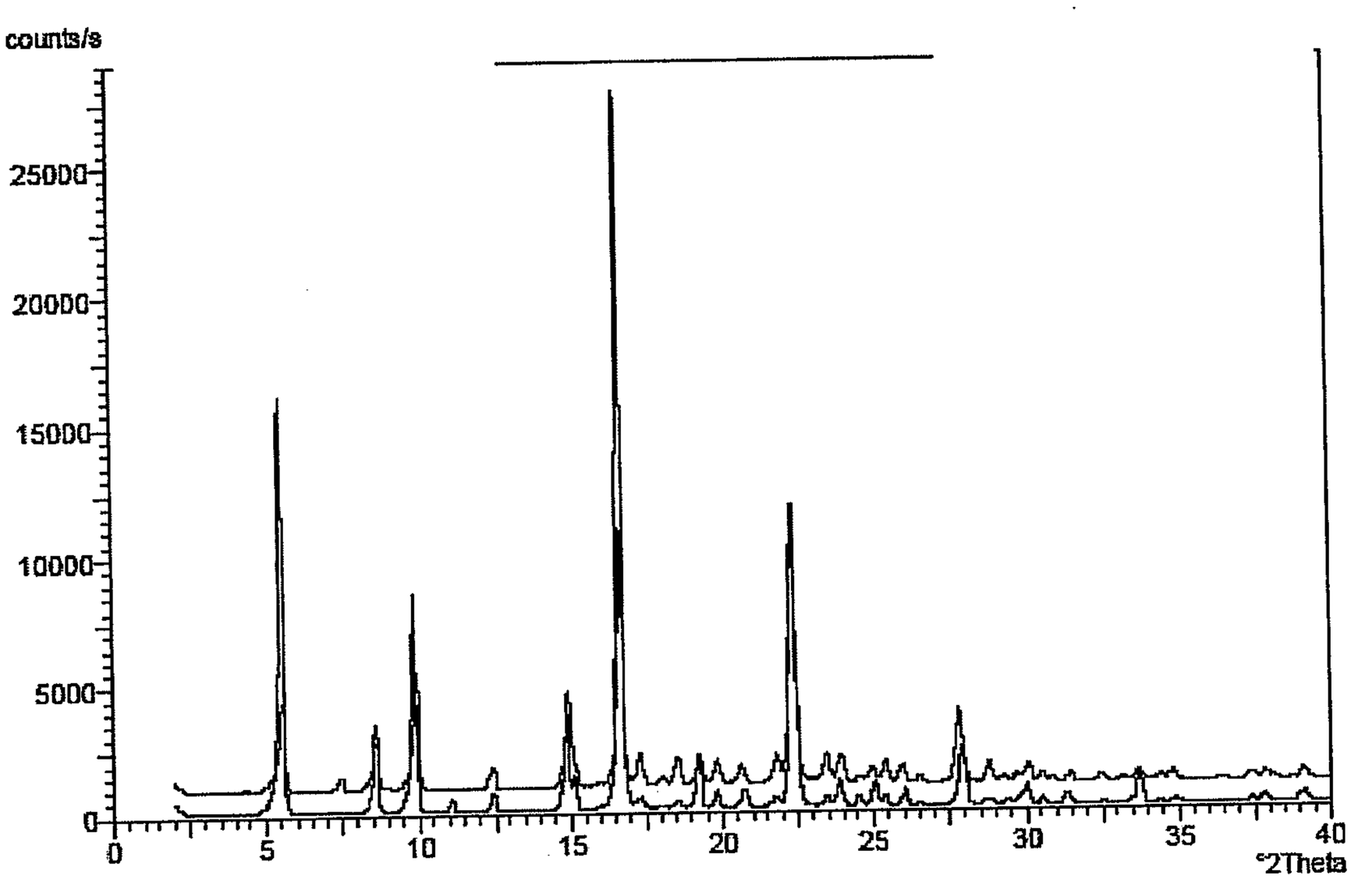


FIGURE 12B

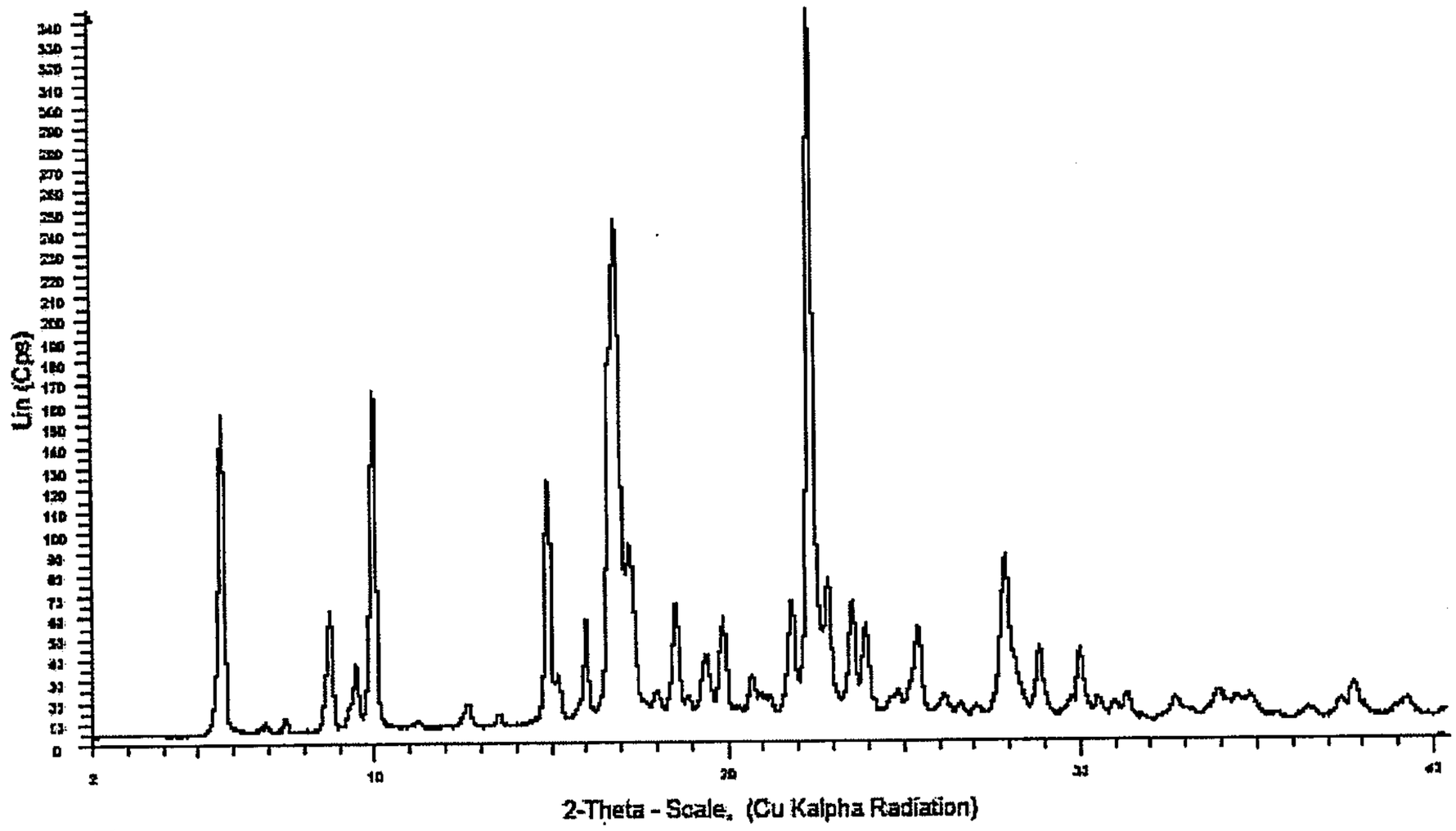


FIGURE 12C

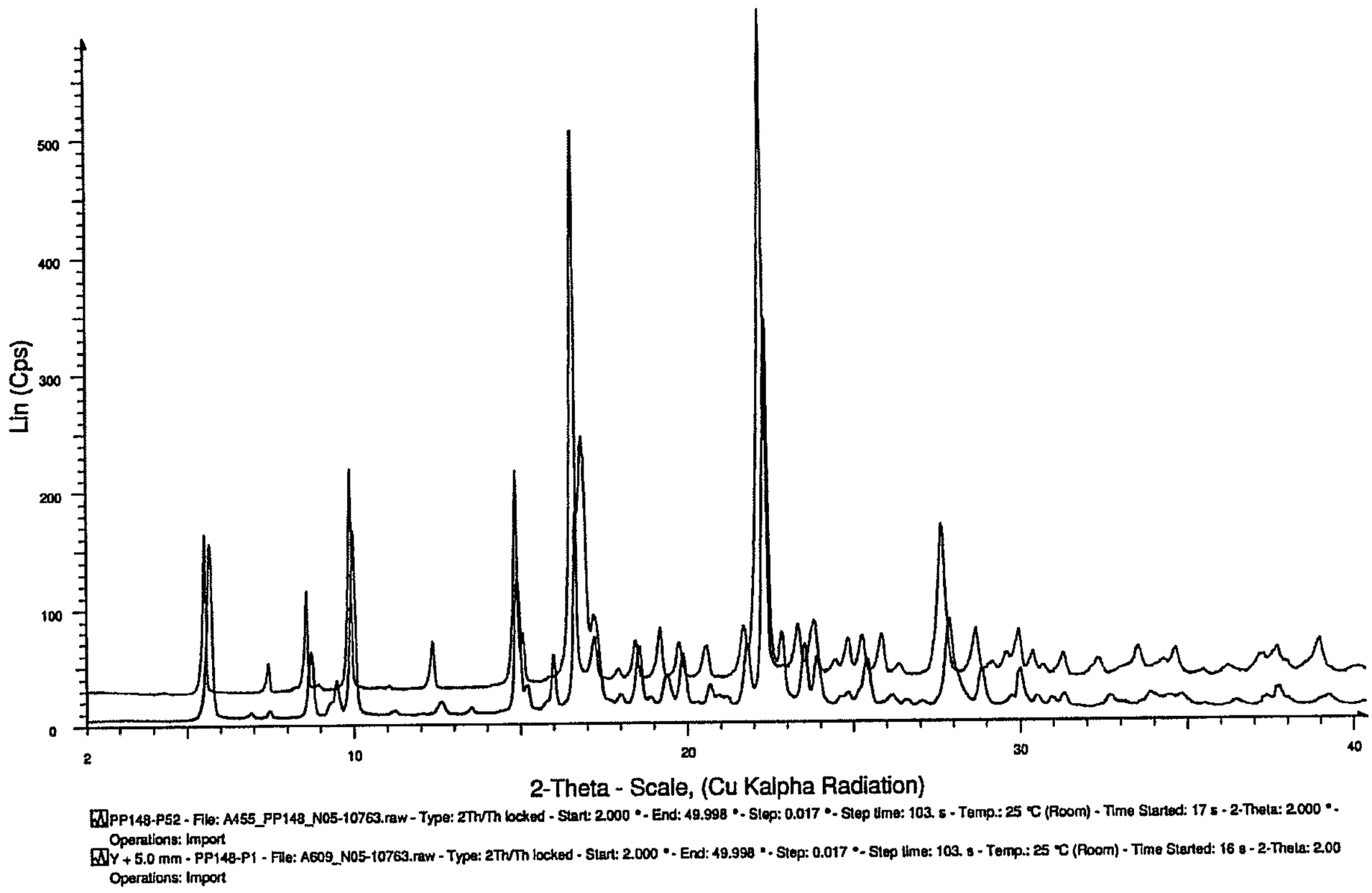


FIGURE 12D

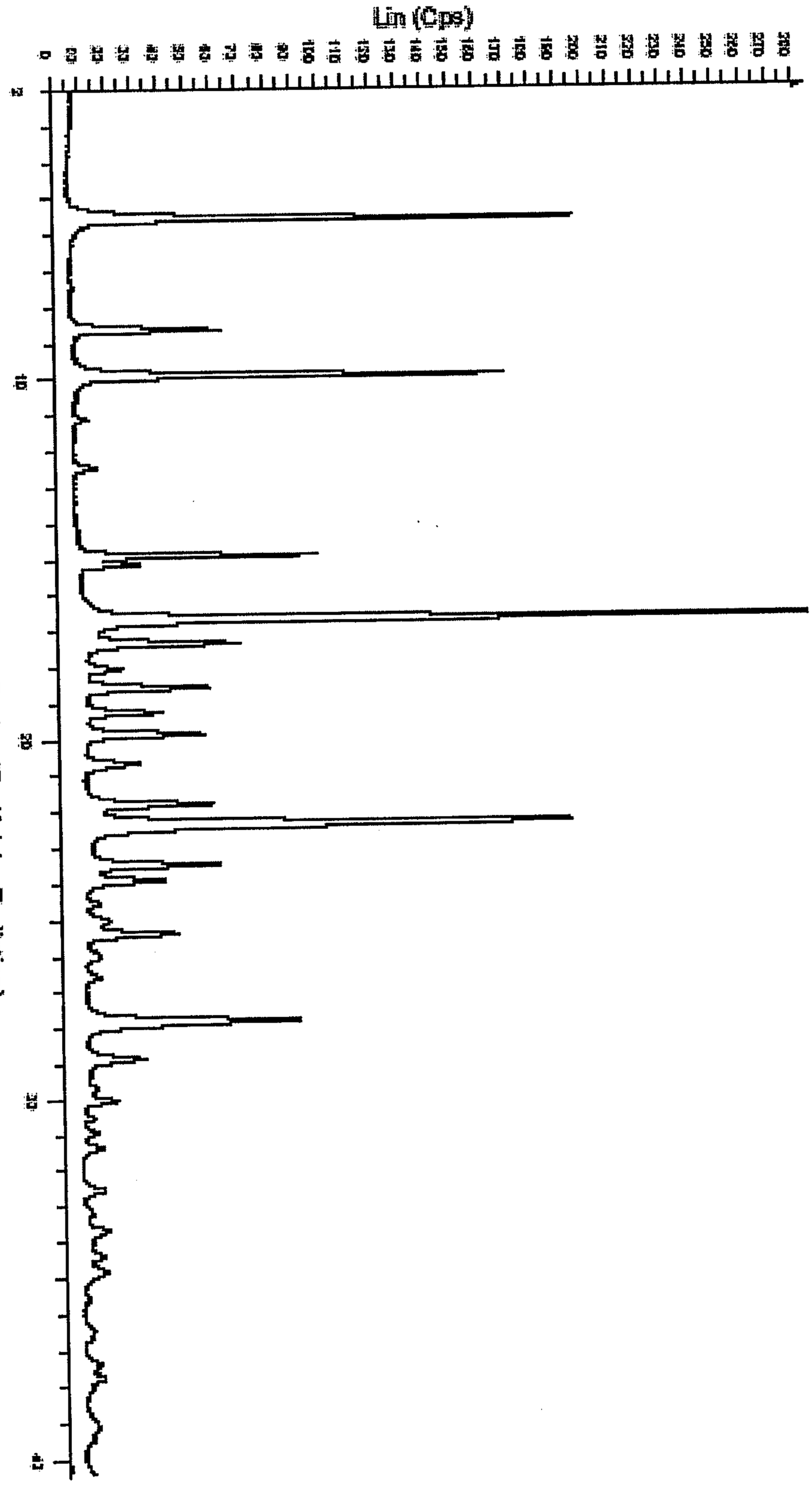

Lin (Cps)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
2-Theta - Scale (Cu Kalpha Radiation)

FIGURE 13A

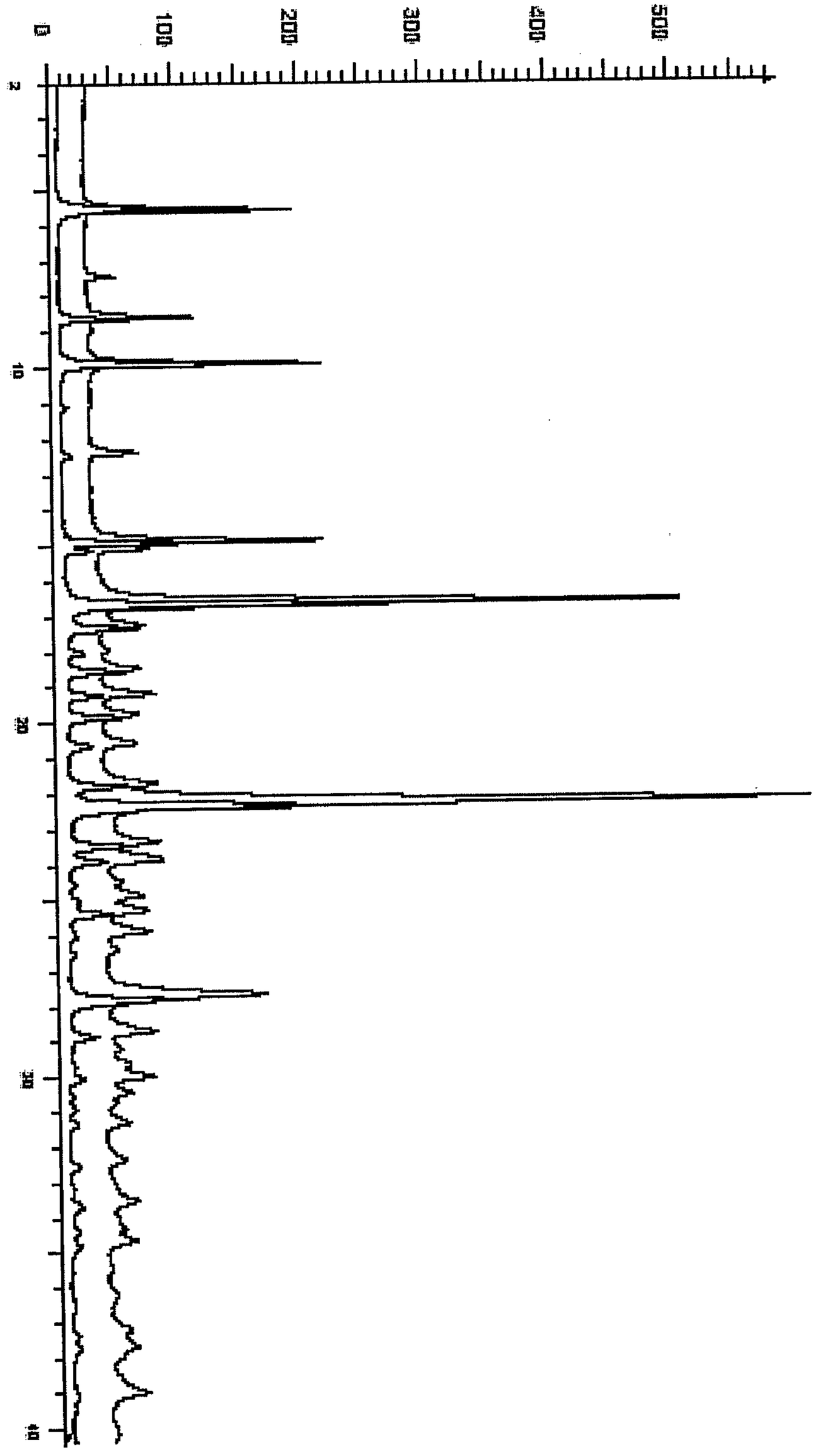

0
100
200
300
400
500
2
10
20
30
40
2-Theta - Scale (Cu Kalpha Radiation)

FIGURE 13B

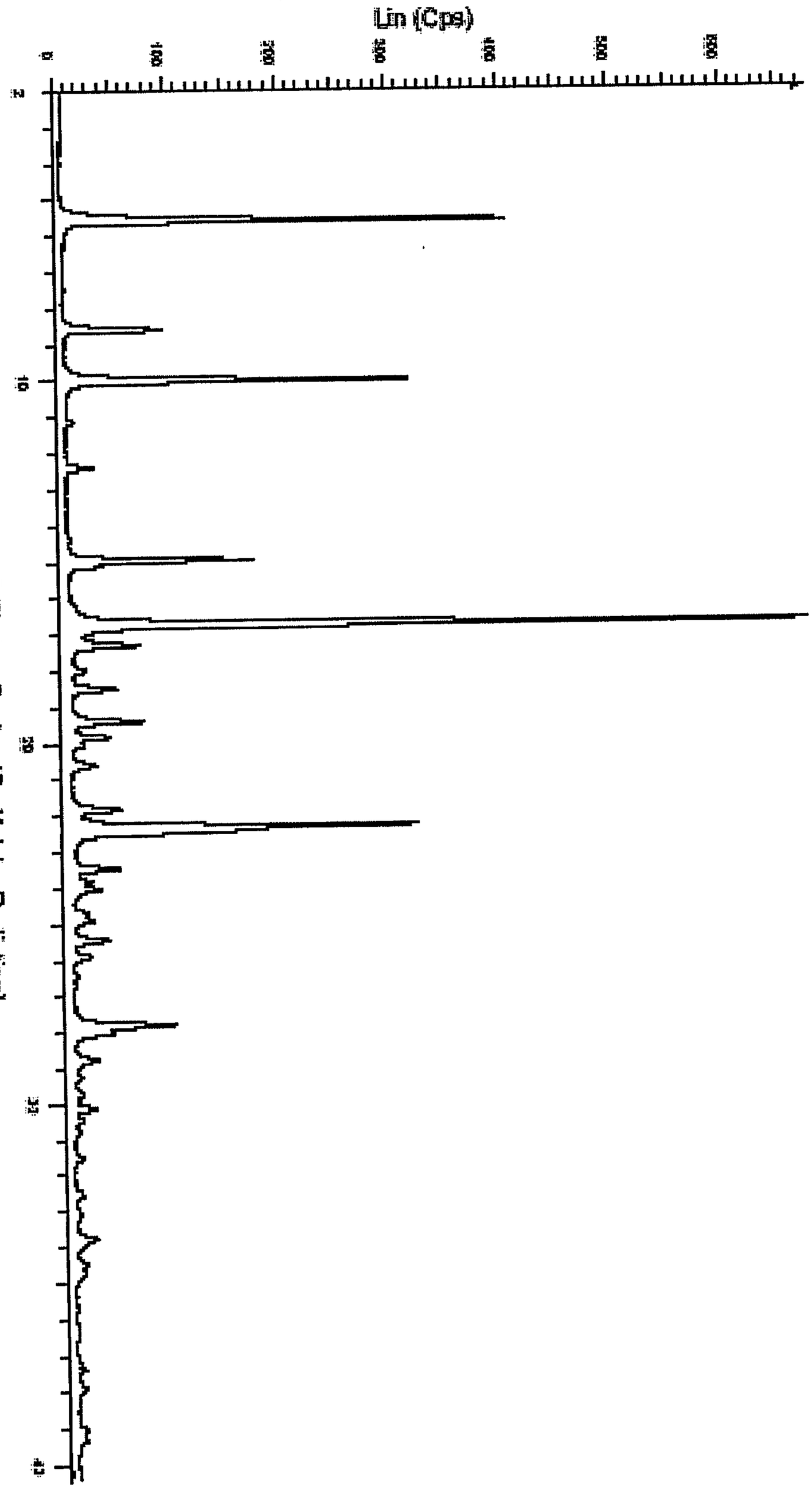


FIGURE 13C

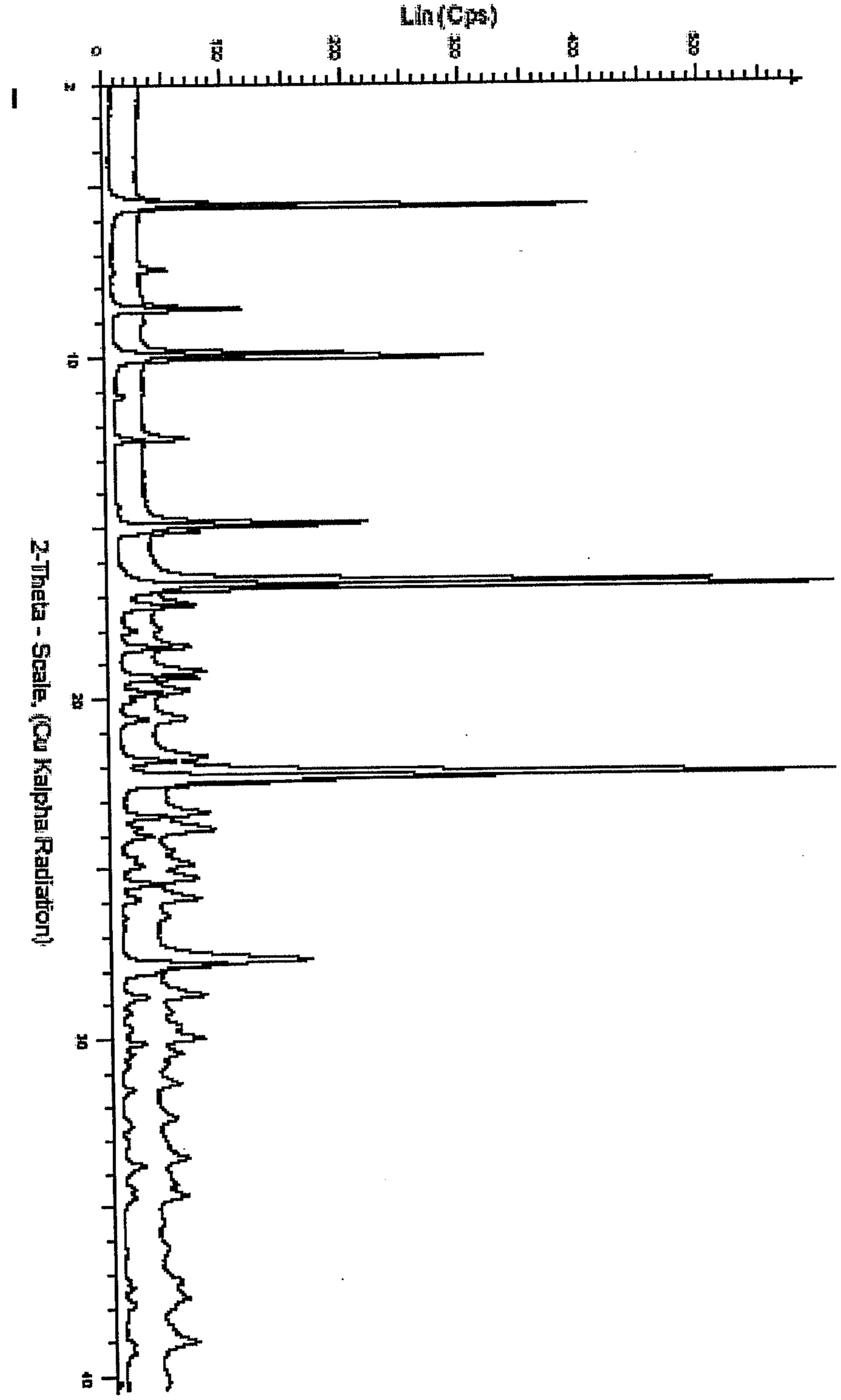


FIGURE 13D

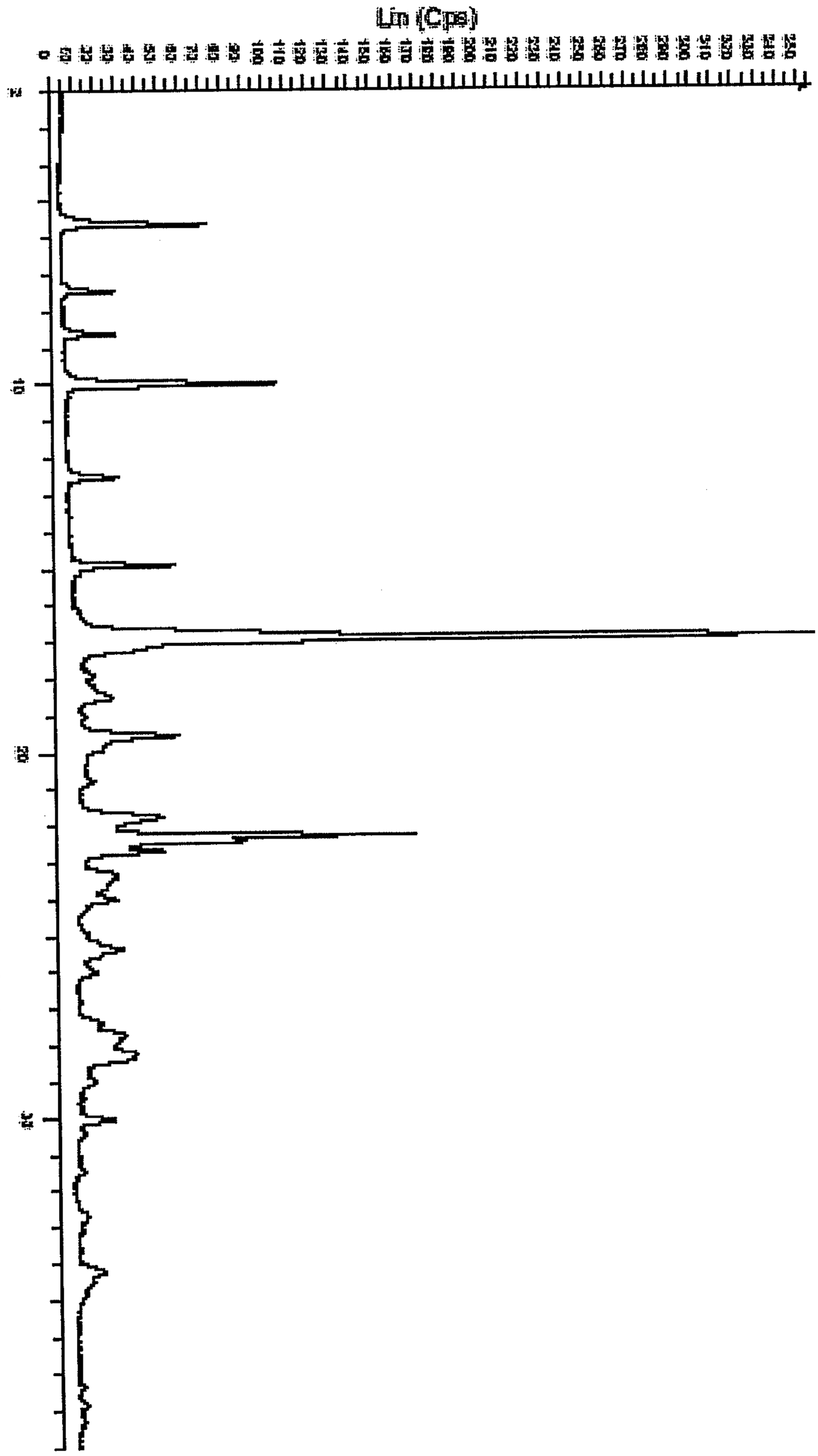


FIGURE 14A

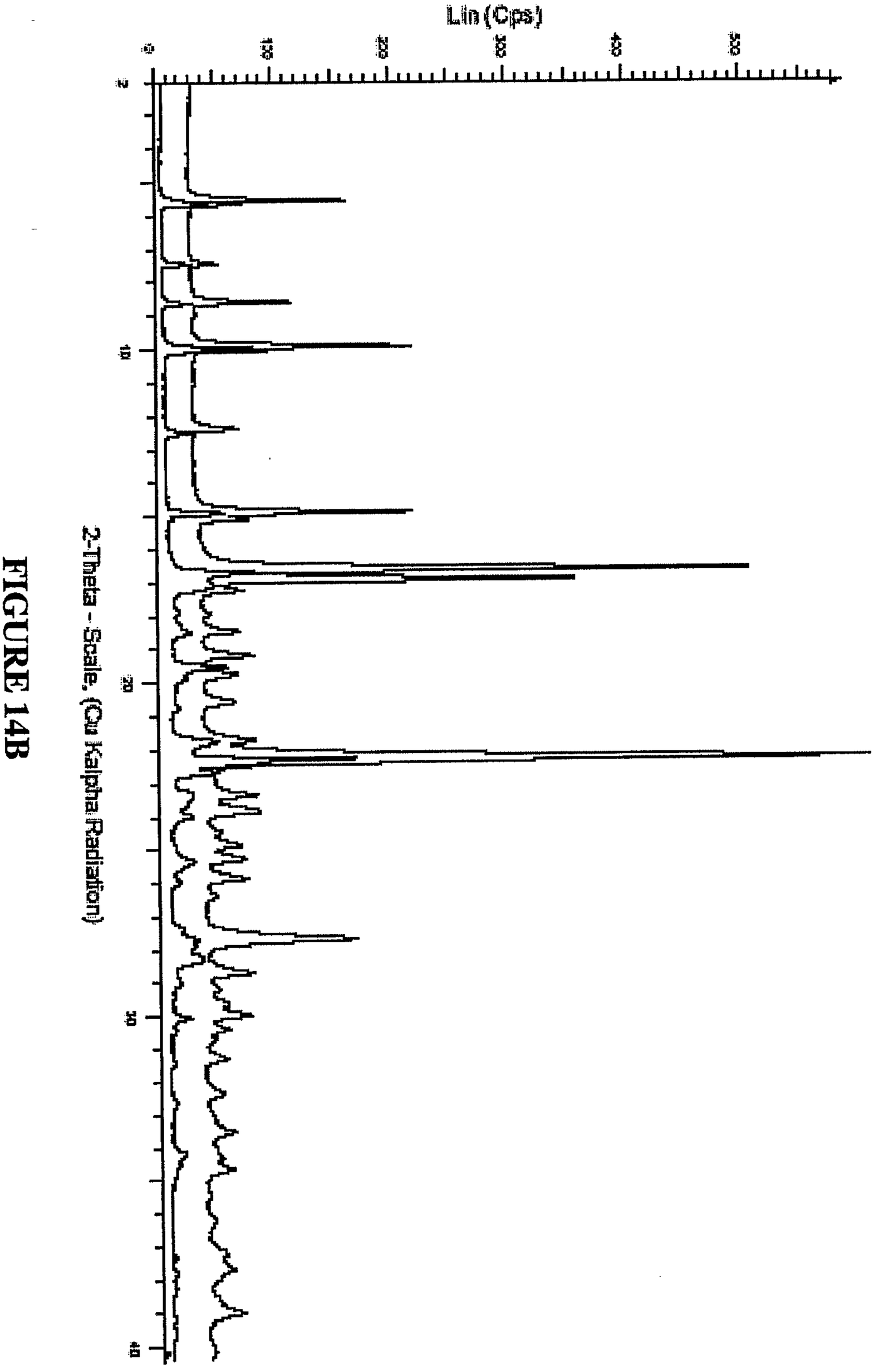

Lin (Cps)
0
100
200
300
400
500
2-Theta - Scale (Cu Kalpha Radiation)
10
20
30
40

FIGURE 14B

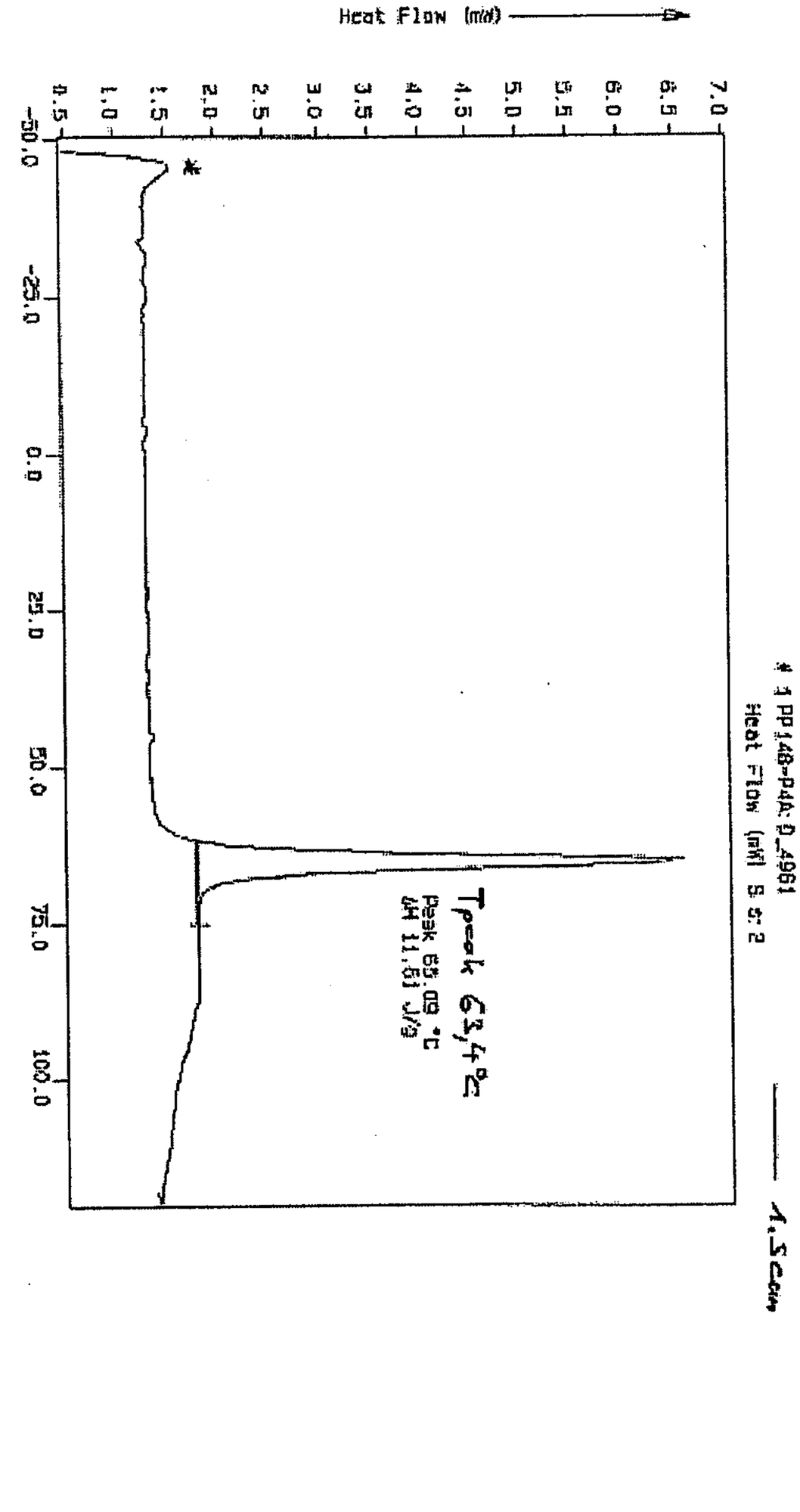

Heat Flow (mW)
1 PP148-P4A: 0_4961
Heat Flow (mW) 5:5:2
Peak 63,4°C
Peak 65,09 °C
ΔH 11,61 J/g
Temperature/°C
-50.0
-25.0
0.0
25.0
50.0
75.0
100.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
1.5 Exo

FIGURE 15

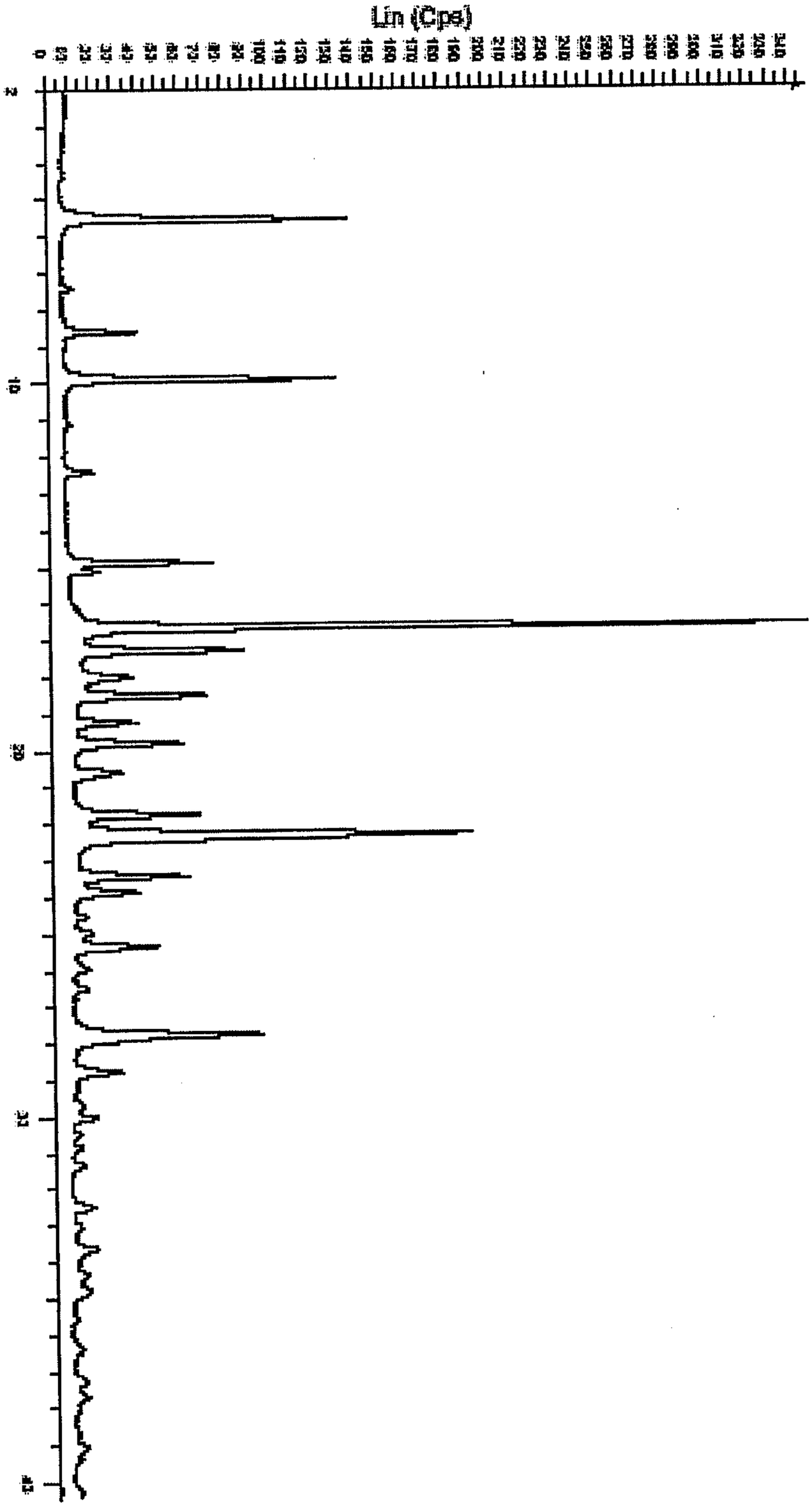


FIGURE 16A

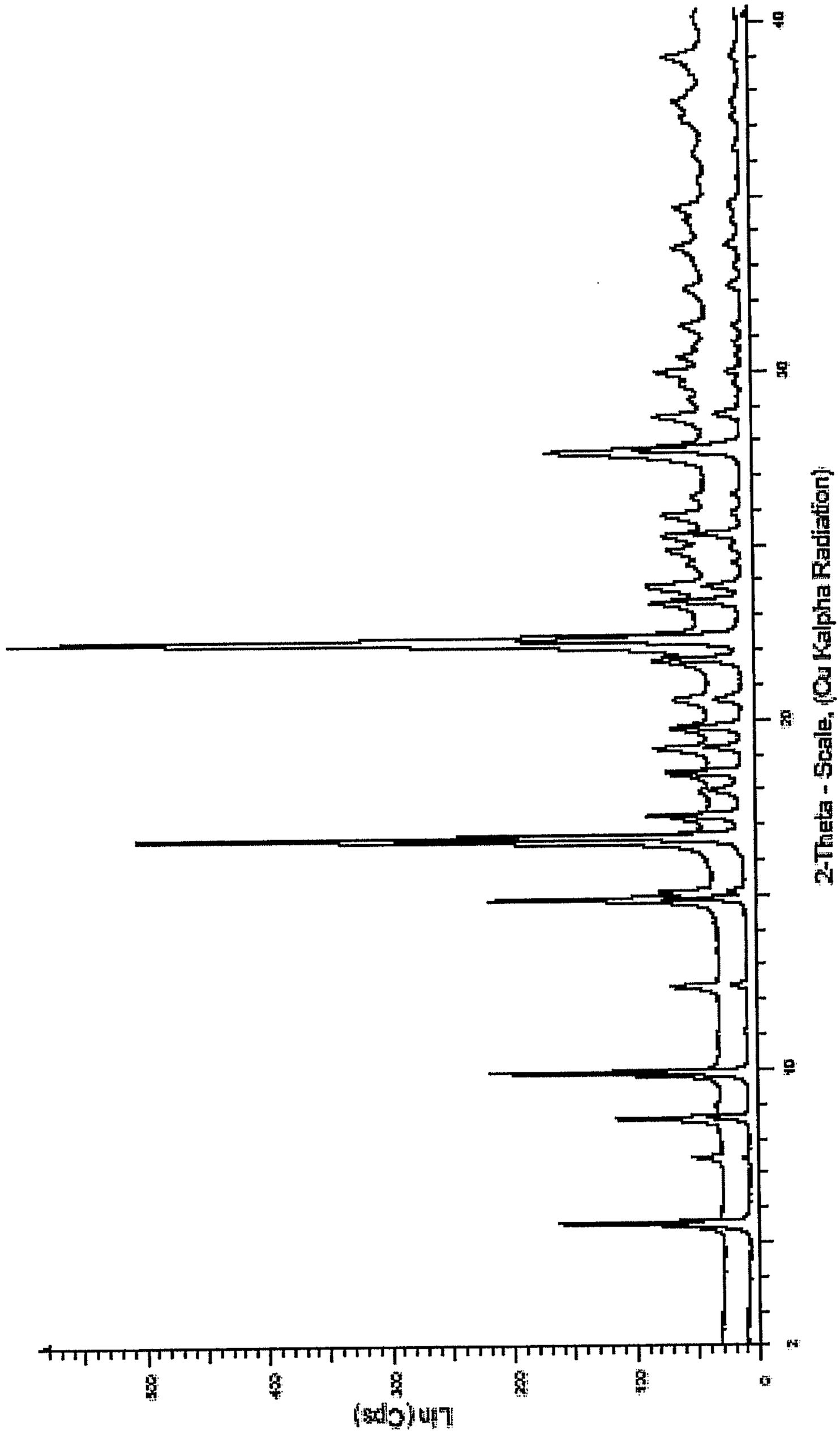


FIGURE 16B

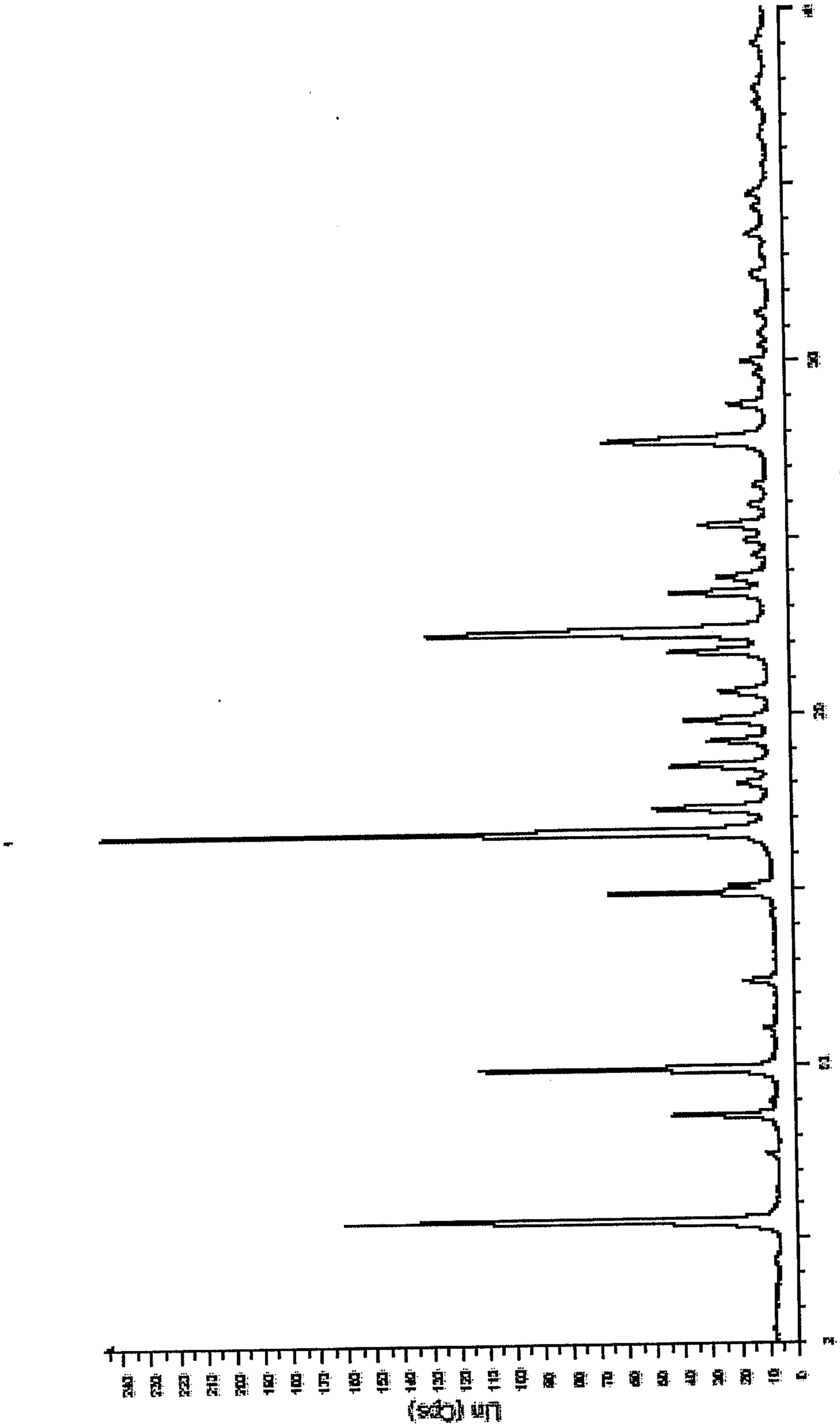


FIGURE 16C

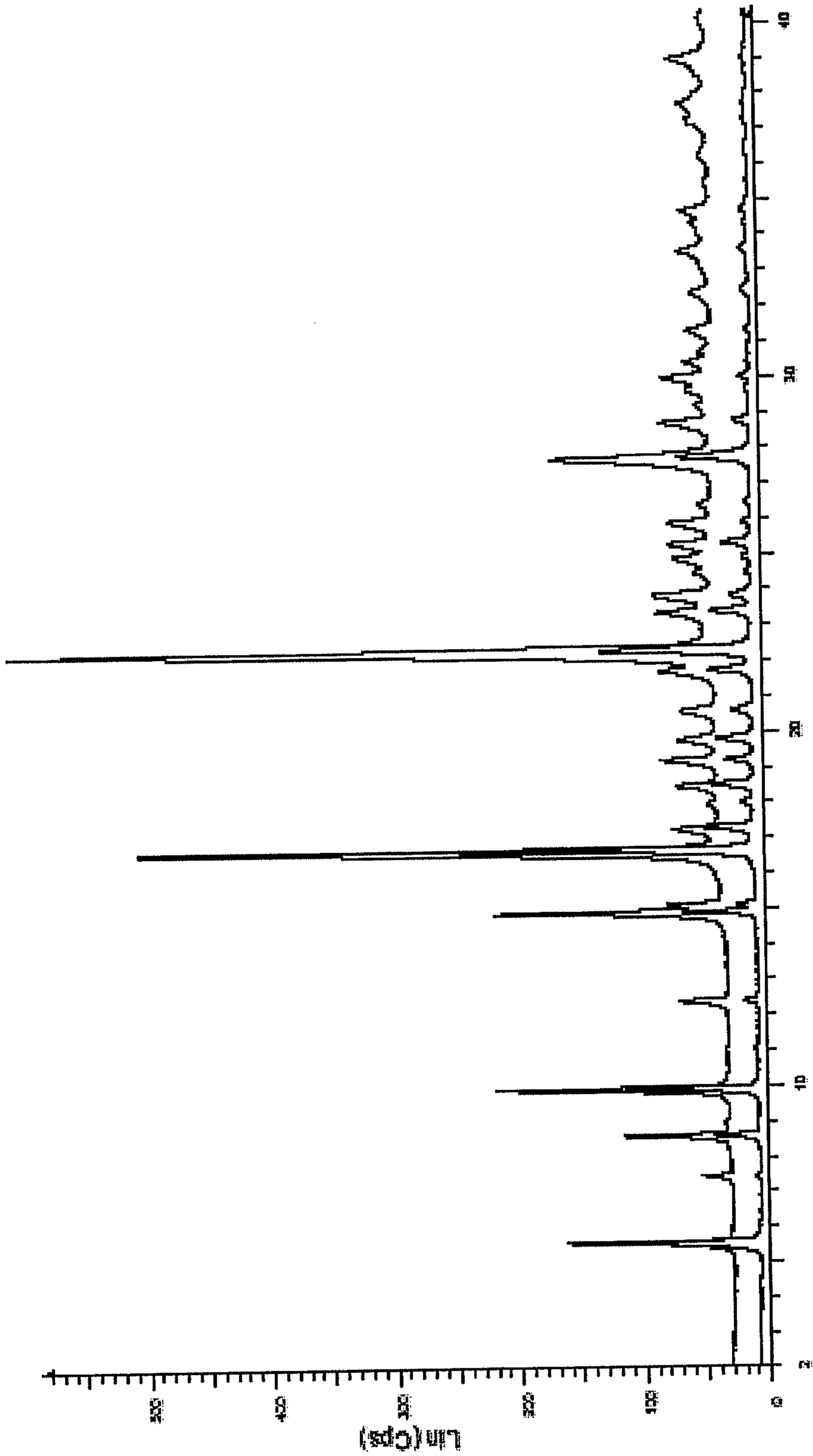


FIGURE 16D

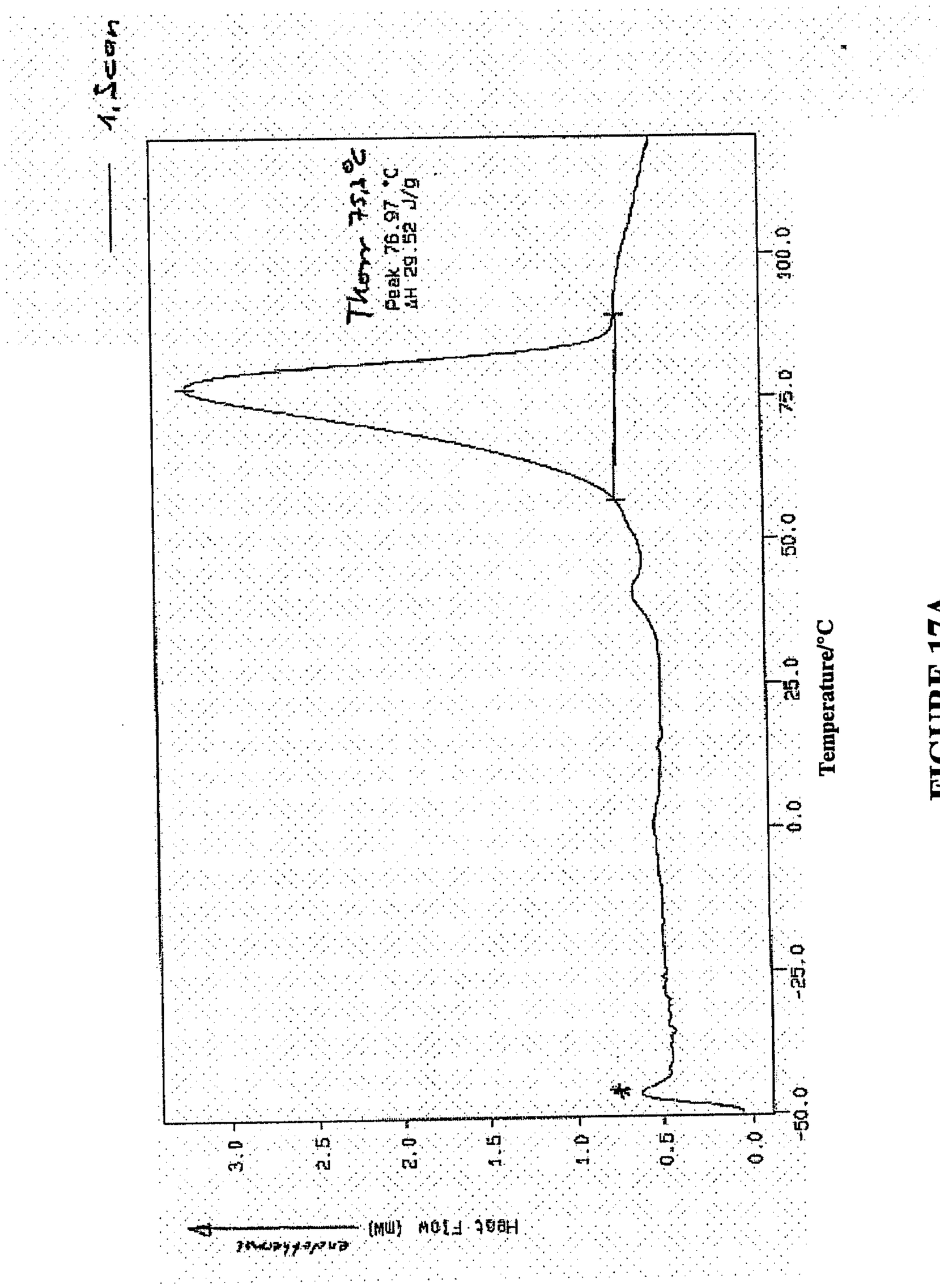

1,2-dcb
Tmax 73.2°C
Peak 76.97 °C
ΔH 29.52 J/g
100.0
75.0
50.0
25.0
0.0
-25.0
-50.0
Temperature/°C
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Heat Flow (mW)
endo-down

FIGURE 17A

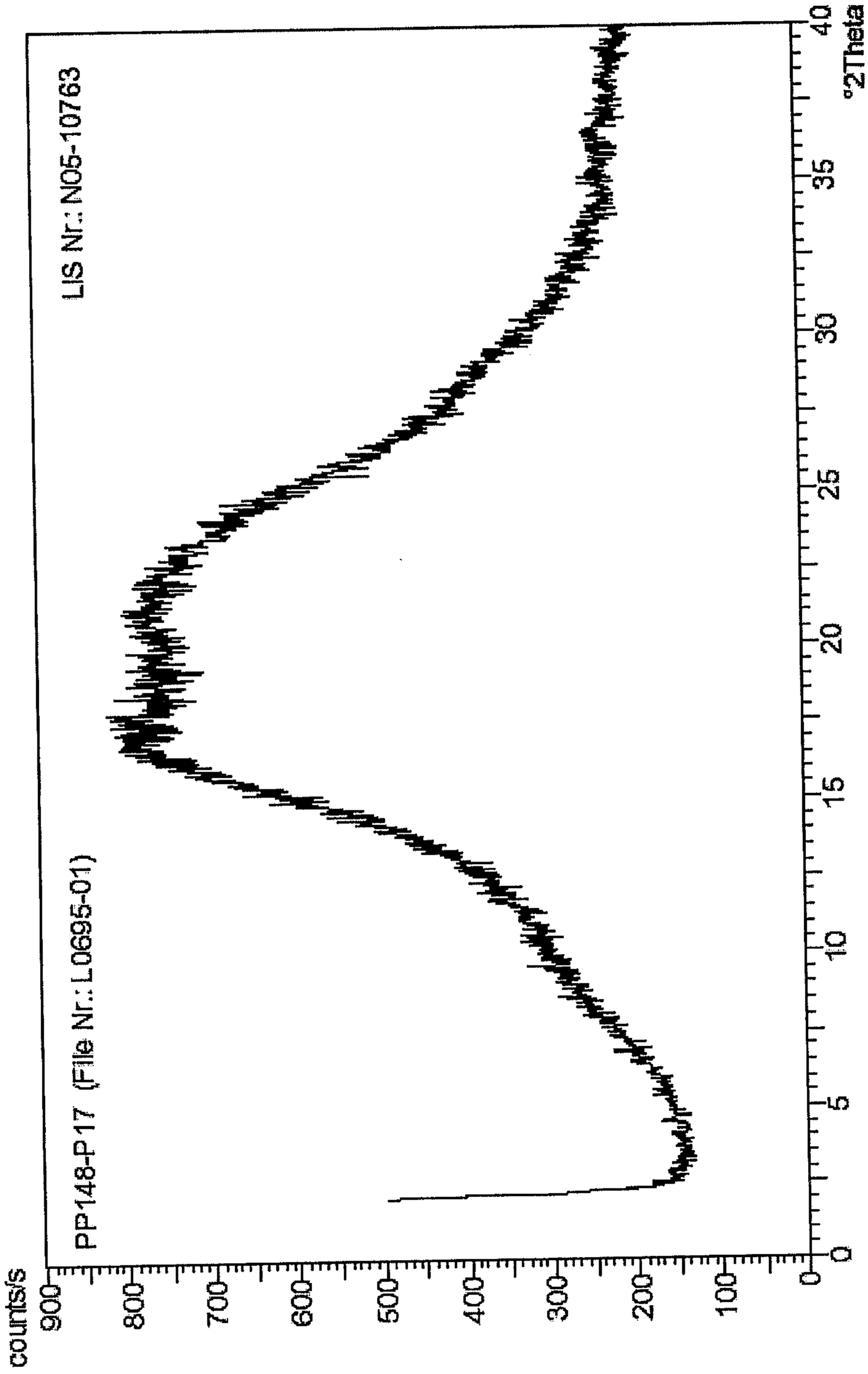

PP148-P17 (File Nr.: L0695-01)
LIS Nr.: N05-10763
counts/s
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
25
30
35
40
°2Theta

FIGURE 17B

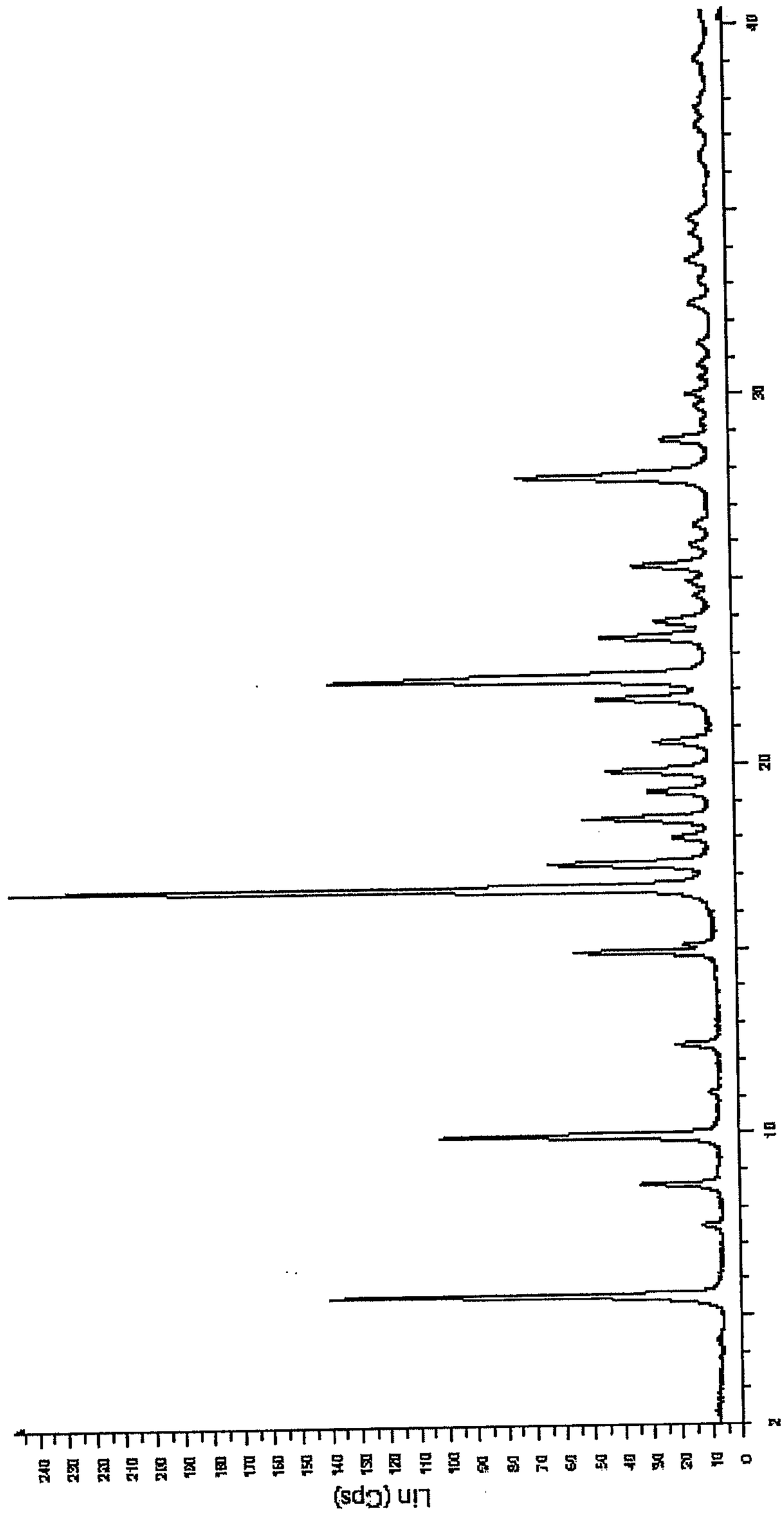


FIGURE 17C

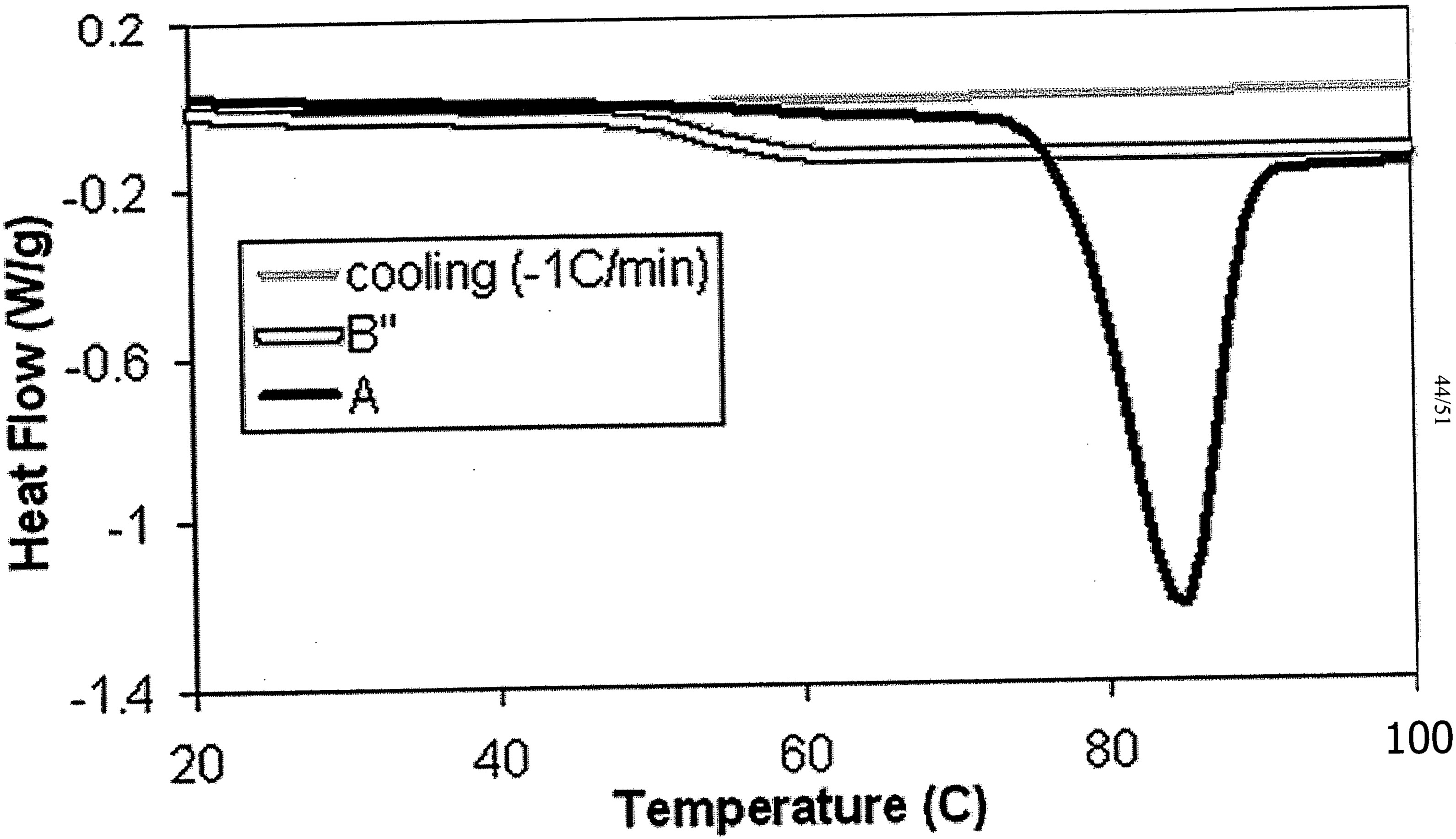


Figure 17D

CA 02886498 2015-03-27

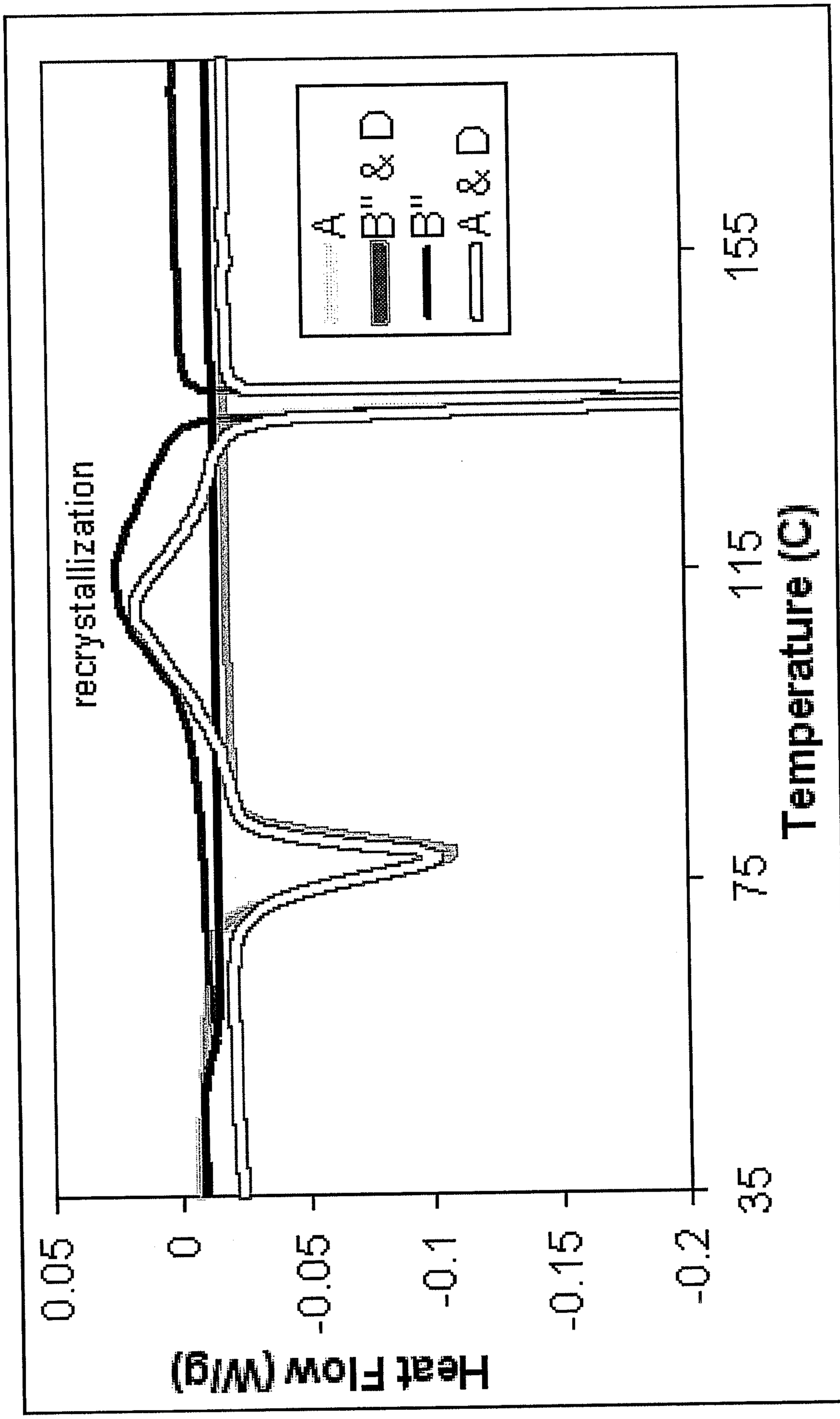

recrystallization
Heat Flow (W/g)
0.05
0
-0.05
-0.1
-0.15
-0.2
35
75
115
155
Temperature (C)

Figure 17E

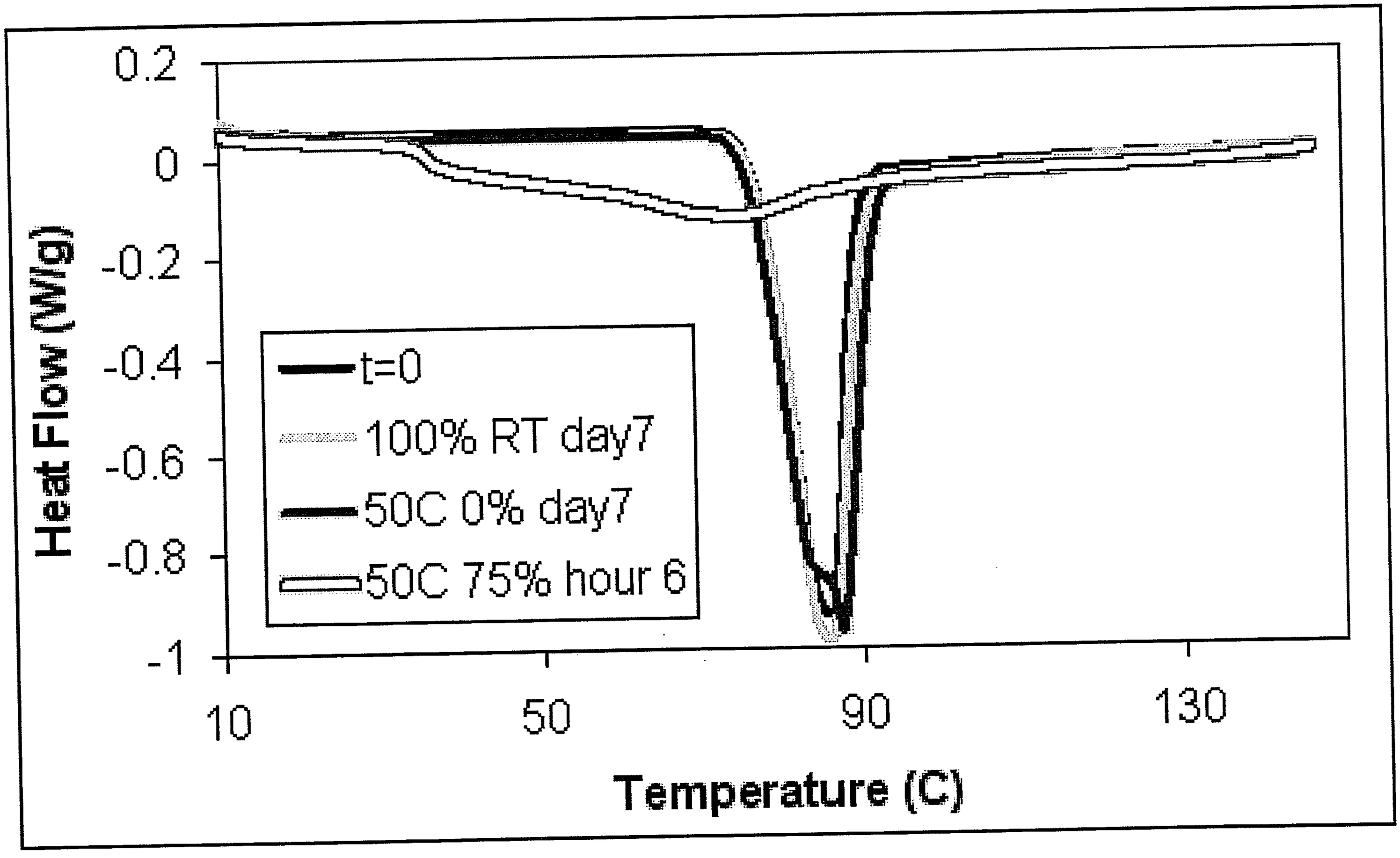


Figure 17F

CA 02886498 2015-03-27

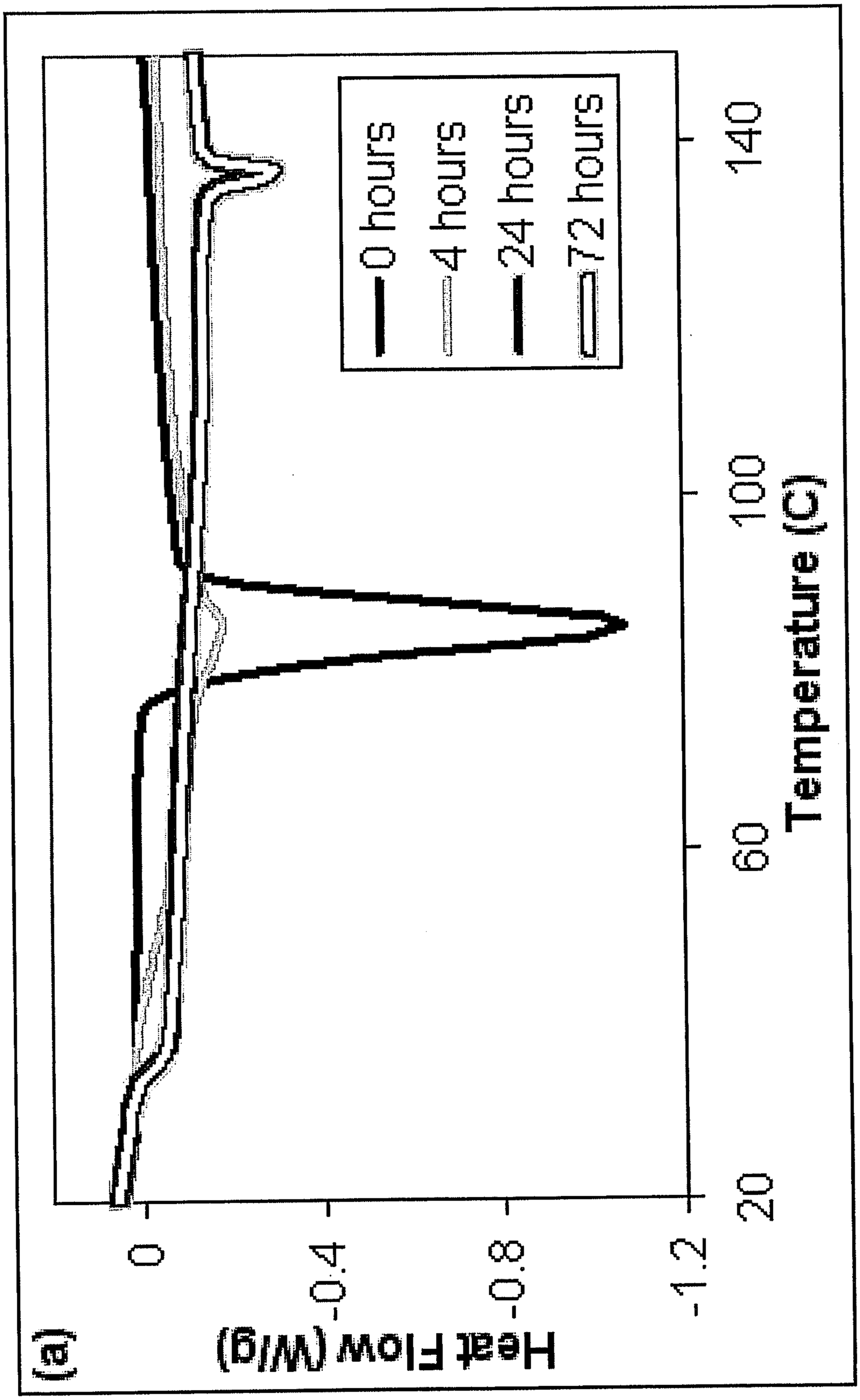

0 hours
4 hours
24 hours
72 hours
140
100
60
20
Temperature (C)
0
-0.4
-0.8
-1.2
Heat Flow (W/g)
Endo

Figure 17G

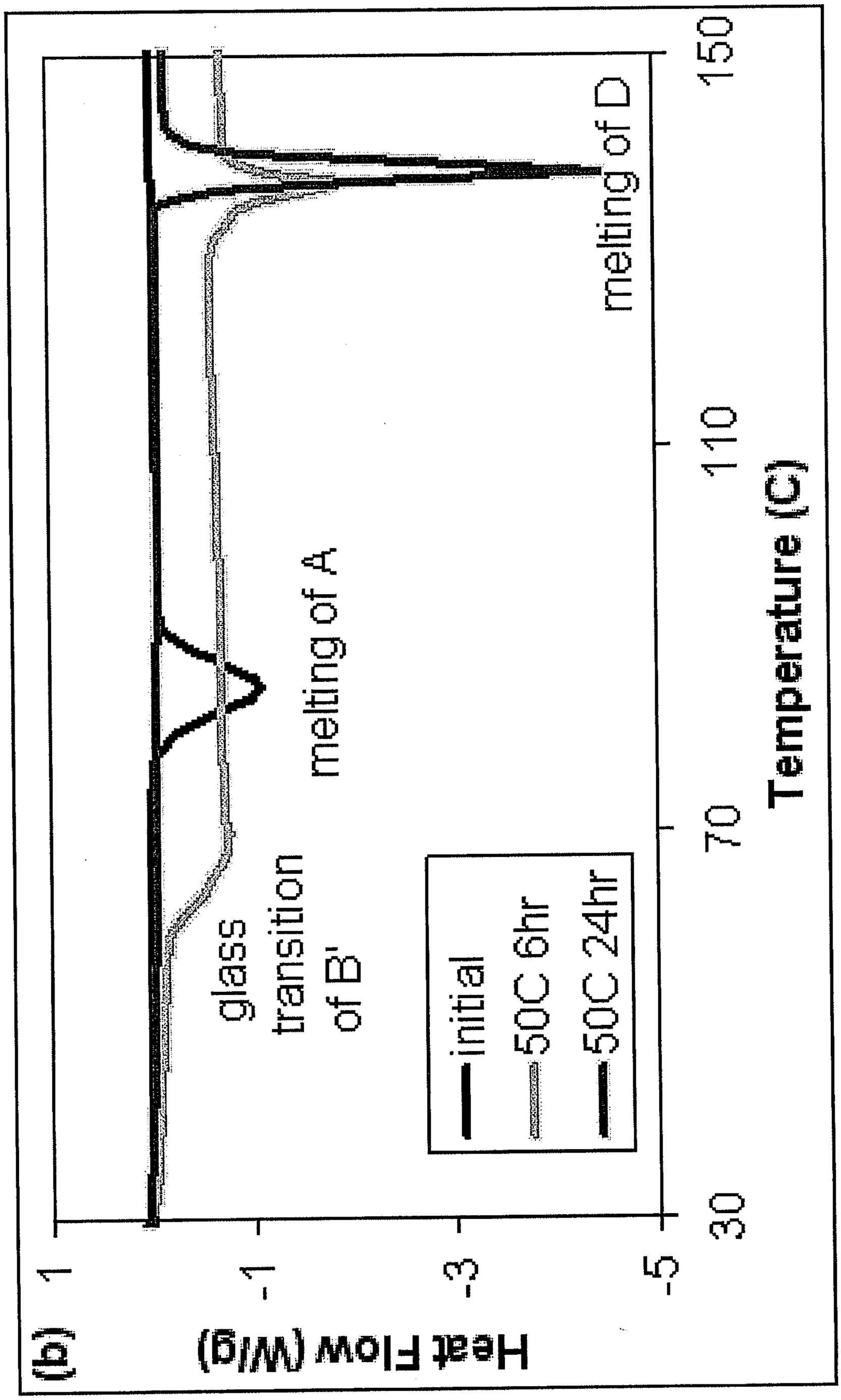

Heat Flow (W/g)
Temperature (C)
glass transition of B'
melting of A
melting of D
initial
50C 6hr
50C 24hr
1
3
5
30
70
110
150

FIGURE 17(b)

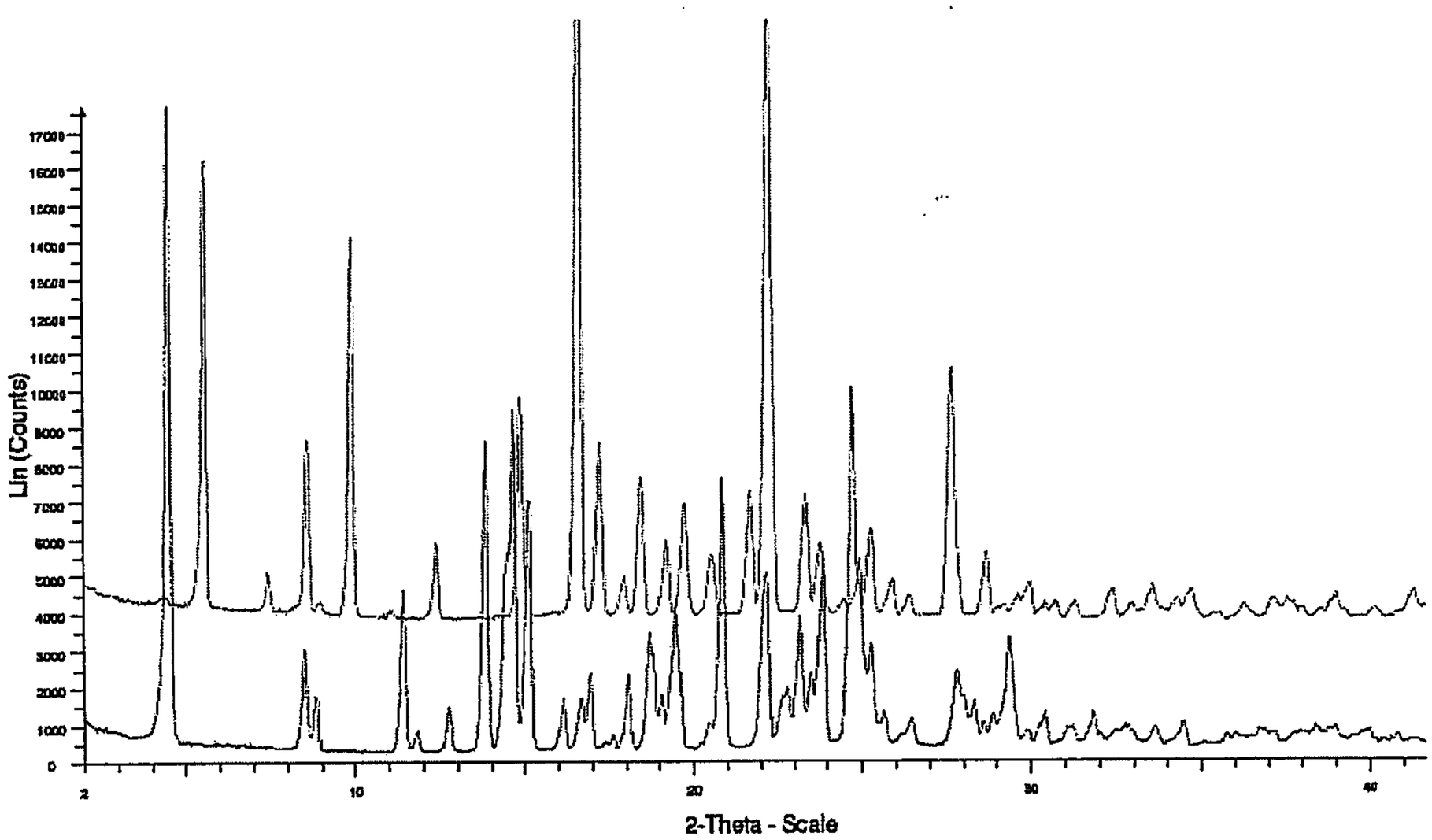

Lin (Counts)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
2-Theta - Scale

FIGURE 18

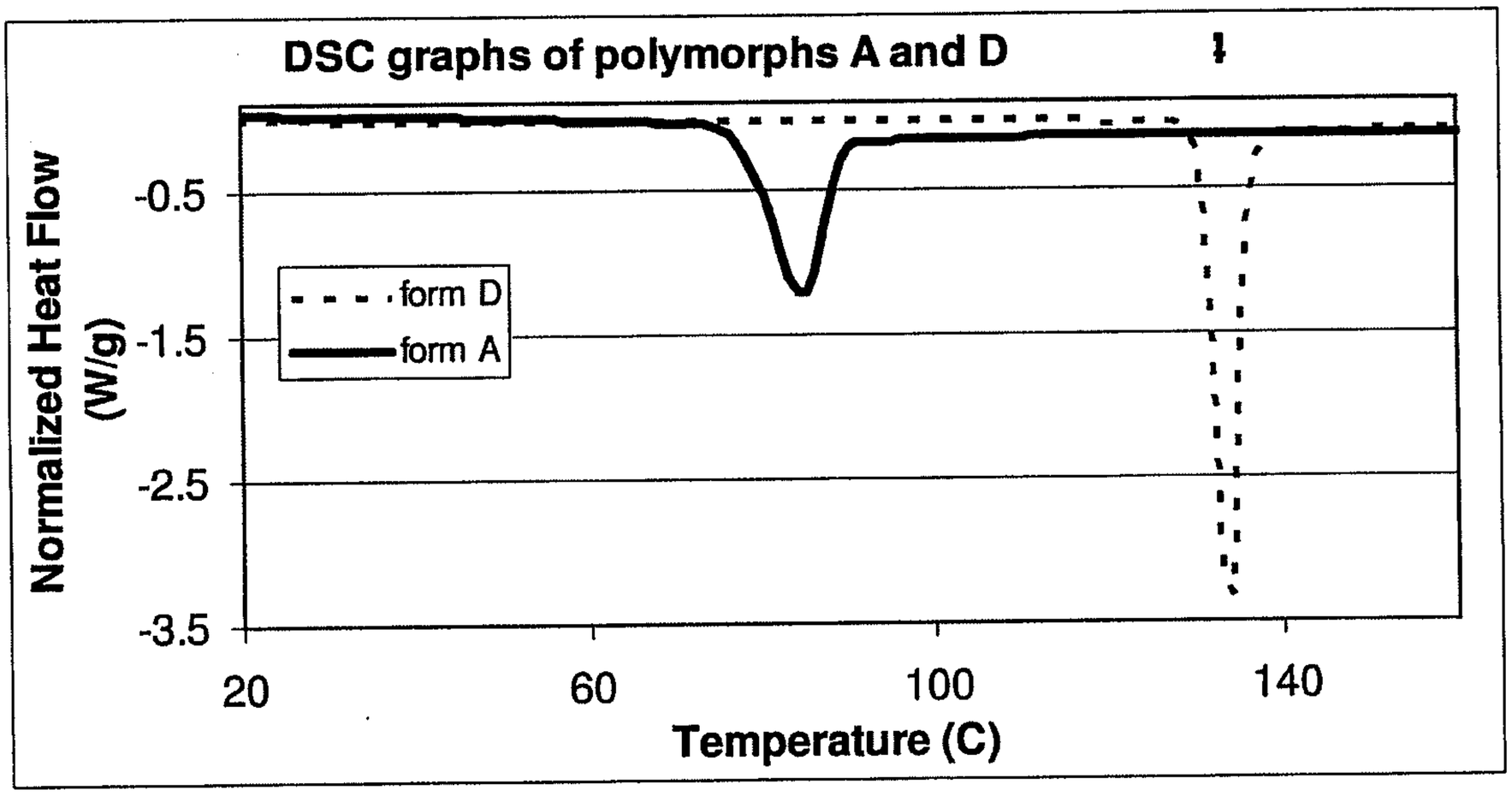

DSC graphs of polymorphs A and D
Normalized Heat Flow (W/g)
-0.5
-1.5
-2.5
-3.5
form D
form A
20
60
100
140
Temperature (C)

FIGURE 19

CA 02886498 2015-03-27

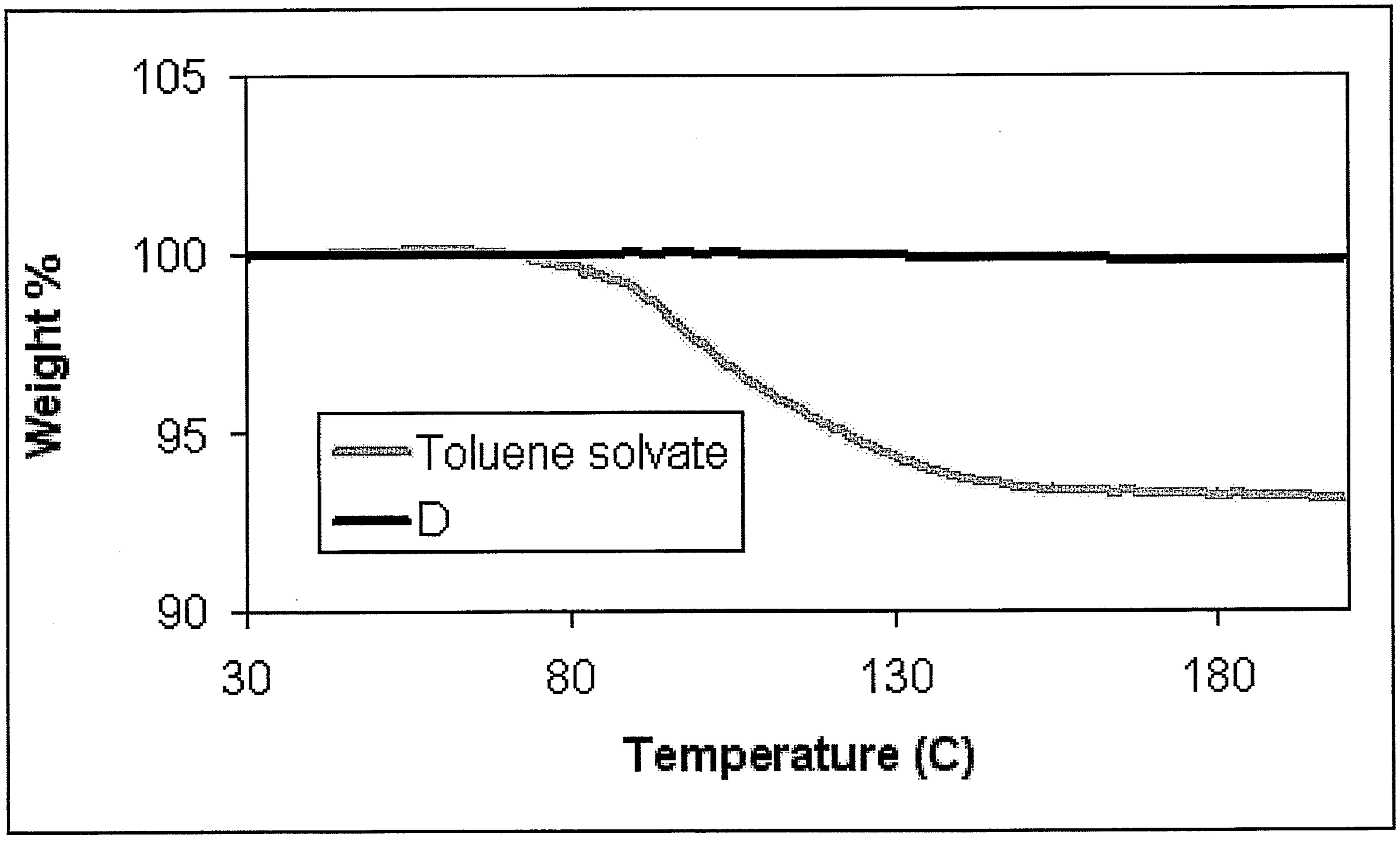
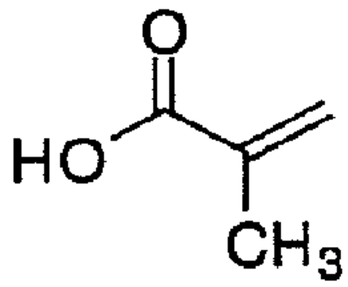
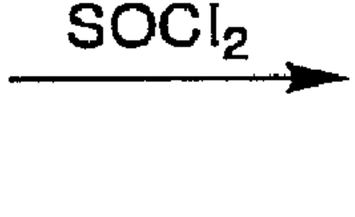
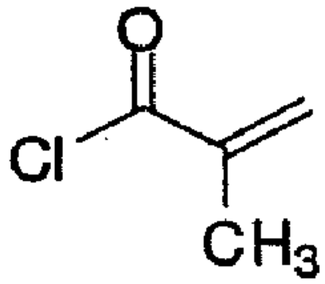
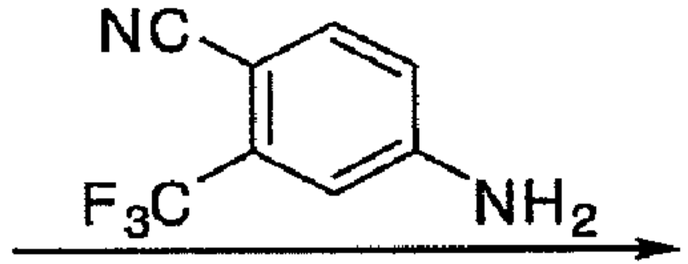


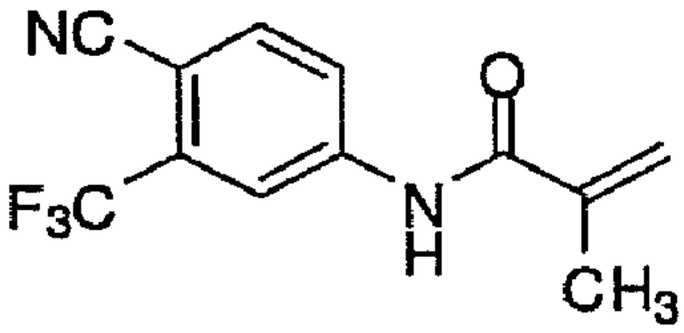
FIGURE 20


HO
O
CH3

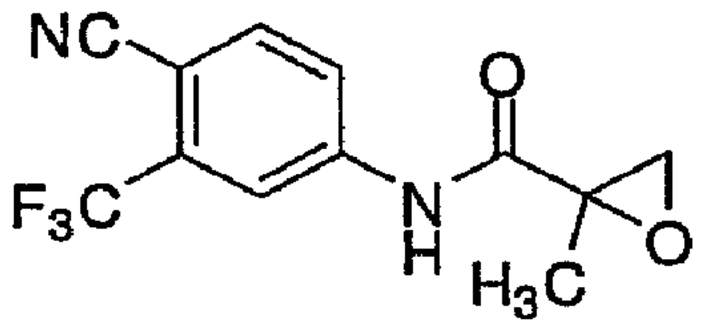

SOCl2

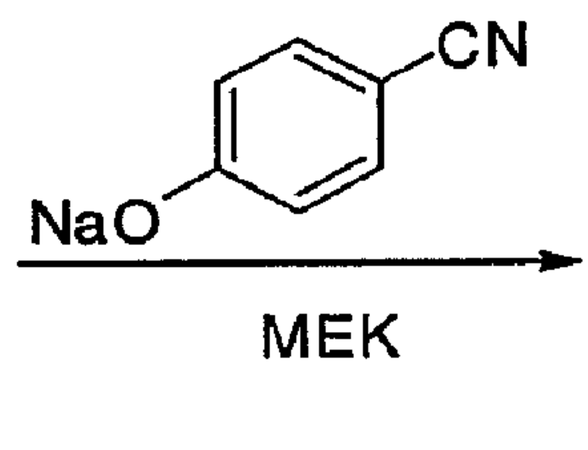

Cl
O
CH3

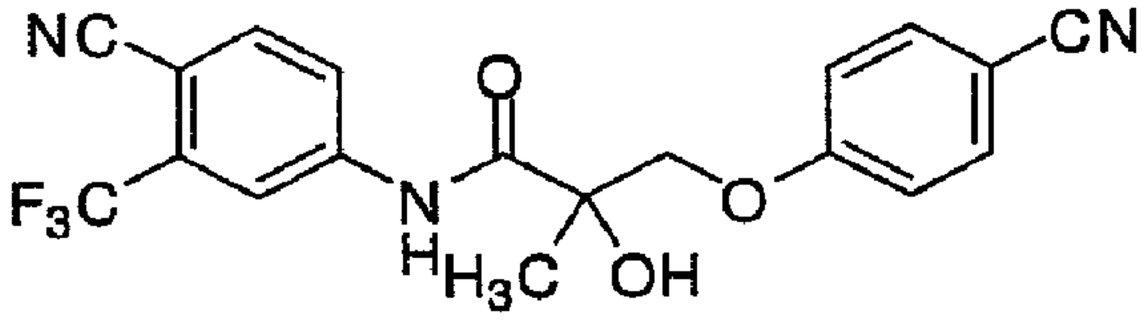

NC
F3C
NH2


NC
F3C
N
H
O
CH3


Ozone


NC
F3C
N
H
O
H3C
O


CN
NaO
MEK


NC
F3C
N
H
O
H3C
OH
O
CN