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(54) Title: TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

**(57) Abrégé/Abstract:**

Provided are polymorphic forms of 5- (ethylsulfonyl) -2- (naphthalen-2-yl) benzo [d] oxazole useful in the treatment of Duchenne muscular dystrophy.

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(54) Title: POLYMORPHS OF A COMPOUND FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

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## TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

### RELATED APPLICATION

Priority is claimed herein to British application GB0715937.9, filed August 15, 2007, entitled "TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY." The above-5 referenced application is incorporated by reference herein in its entirety.

### FIELD

Provided are polymorphic forms of a compound for the treatment of Duchenne muscular dystrophy.

### BACKGROUND

10 Duchenne muscular dystrophy (DMD) is a common, genetic neuromuscular disease associated with the progressive deterioration of muscle function, first described over 150 years ago by the French neurologist, Duchenne de Boulogne, after whom the disease is named. DMD has been characterized as an X-linked recessive disorder that affects 1 in 3,500 males caused by mutations in the dystrophin gene. The gene is the largest in the human 15 genome, encompassing 2.6 million base pairs of DNA and containing 79 exons. Approximately 60% of dystrophin mutations are large insertion or deletions that lead to frameshift errors downstream, whereas approximately 40% are point mutations or small frameshift rearrangements. The vast majority of DMD patients lack the dystrophin protein. Becker muscular dystrophy is a much milder form of DMD caused by reduction in the 20 amount, or alteration in the size, of the dystrophin protein. The high incidence of DMD (1 in 10,000 sperm or eggs) means that genetic screening will never eliminate the disease, so an effective therapy is highly desirable.

25 A number of natural and engineered animal models of DMD exist, and provide a mainstay for preclinical studies (Allamand, V. & Campbell, K. P. Animal models for muscular dystrophy: valuable tools for the development of therapies. *Hum. Mol. Genet.* **9**, 2459-2467 (2000). Although the mouse, cat and dog models all have mutations in the *DMD* gene and exhibit a biochemical dystrophinopathy similar to that seen in humans, they show 30 surprising and considerable variation in terms of their phenotype. Like humans, the canine (Golden retriever muscular dystrophy and German short-haired pointer) models have a severe phenotype; these dogs typically die of cardiac failure. Dogs offer the best phenocopy for human disease, and are considered a high benchmark for preclinical studies. Unfortunately,

breeding these animals is expensive and difficult, and the clinical time course can be variable among litters.

The *mdx* mouse is the most widely used model due to availability, short gestation time, time to mature and relatively low cost (Bulfield, G., Siller, W. G., Wight, P. A. & Moore, K. J. X chromosome-linked muscular dystrophy (*mdx*) in the mouse. *Proc. Natl Acad. Sci. USA* **81**, 1189-1192 (1984)).

Since the discovery of the DMD gene about 20 years ago, varying degrees of success in the treatment of DMD have been achieved in preclinical animal studies, some of which are being followed up in humans. Present therapeutic strategies can be broadly divided into three groups: first, gene therapy approaches; second, cell therapy; and last, pharmacological therapy. Gene- and cell-based therapies offer the fundamental advantage of obviating the need to separately correct secondary defects/ pathology (for example, contractures), especially if initiated early in the course of the disease. Unfortunately, these approaches face a number of technical hurdles. Immunological responses against viral vectors, myoblasts and newly synthesized dystrophin have been reported, in addition to toxicity, lack of stable expression and difficulty in delivery.

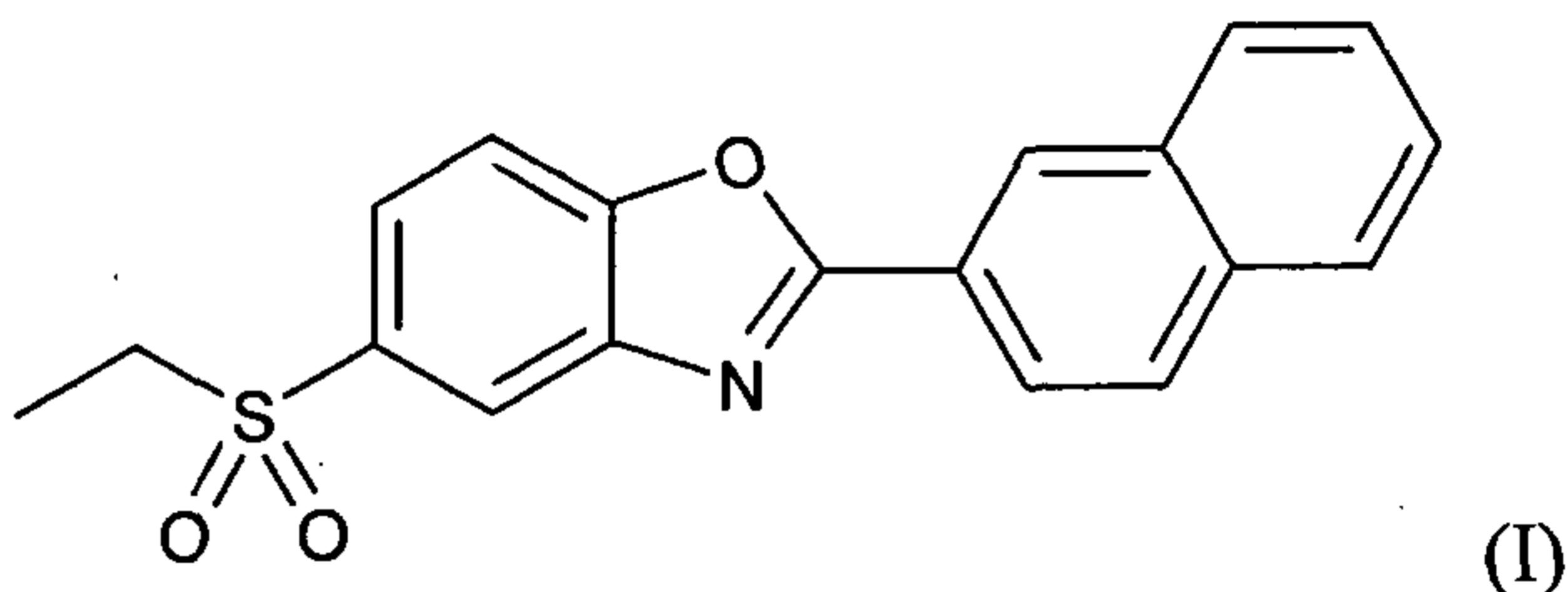
Pharmacological approaches for the treatment of muscular dystrophy differ from gene- and cell-based approaches in not being designed to deliver either the missing gene and/or protein. In general, the pharmacological strategies use drugs/molecules in an attempt to improve the phenotype by means such as decreasing inflammation, improving calcium homeostasis and increasing muscle progenitor proliferation or commitment. These strategies offer the advantage that they are easy to deliver systemically and can circumvent many of the immunological and/or toxicity issues that are related to vectors and cell-based therapies. Although investigations with corticosteroids and sodium cromoglycate, to reduce inflammation, dantrolene to maintain calcium homeostasis and clenbuterol to increase muscle strength, have produced promising results none of these potential therapies has yet been shown to be effective in treating DMD.

An alternative pharmacological approach is upregulation therapy. Upregulation therapy is based on increasing the expression of alternative genes to replace a defective gene and is particularly beneficial when an immune response is mounted against a previously absent protein. Upregulation of utrophin, an autosomal parologue of dystrophin has been proposed as a potential therapy for DMD (Perkins & Davies, Neuromuscul Disord, S1: S78-

S89 (2002), Khurana & Davies, *Nat Rev Drug Discov* 2:379-390 (2003)). When utrophin is overexpressed in transgenic *mdx* mice it localizes to the sarcolemma of muscle cells and restores the components of the dystrophin-associated protein complex (DAPC), which prevents the dystrophic development and in turn leads to functional improvement of skeletal muscle. Adenoviral delivery of utrophin in the dog has been shown to prevent pathology. Commencement of increased utrophin expression shortly after birth in the mouse model can be effective and no toxicity is observed when utrophin is ubiquitously expressed, which is promising for the translation of this therapy to humans. Upregulation of endogenous utrophin to sufficient levels to decrease pathology might be achieved by the delivery of small diffusible compounds.

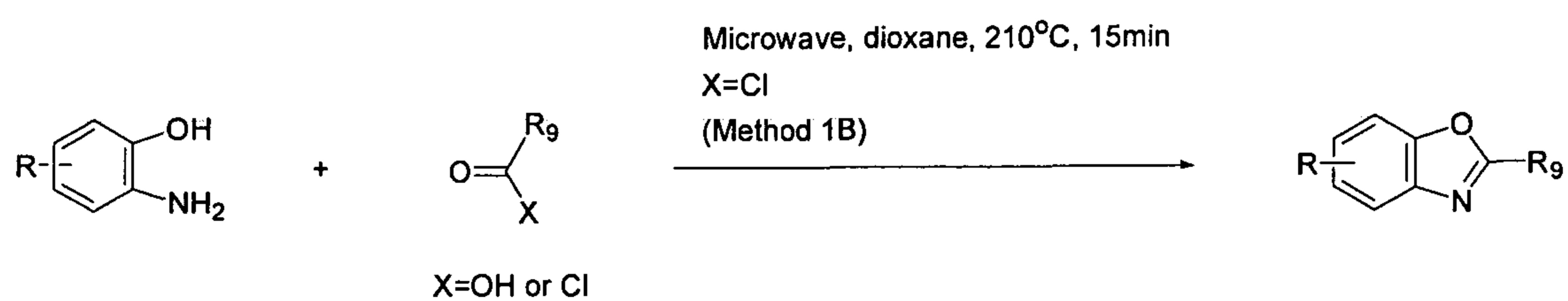
## DESCRIPTION

It has been discovered that the compound of formula I (5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole) has excellent properties for the treatment of Duchenne muscular dystrophy (see, e.g., international patent application publication no. WO 15 2007/091106).



The compound of formula I ( $R = 5$ -ethylsulfonyl;  $R_9 = 2$ -naphthalen-2-yl) may be synthesised according to the following procedure, as disclosed in WO 2007/091106 (page 51):

20



Method 1B is detailed on pages 67-68 in relation to 2-benzyl-5-nitrobenzo[d]oxazole as follows:

**“Method 1B (Compounds I)**

**2-Benzyl-5-nitrobenzo[d]oxazole**

To 2-amino-4-nitrophenol (300mg, 1.95mmol) in dioxane (2.5mL) was added 2-phenylacetyl chloride (290 $\mu$ L, 2.15mmol) at room temperature. The reaction vessel was heated in the microwave at 210°C for 15min. After cooling, the mixture was slowly poured into 1M aqueous sodium hydroxide (50mL), and the resulting precipitate filtered and washed with water. The resulting solid was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 1:7 v/v to ethyl acetate/hexanes 1:5 v/v) to afford 165mg (33%) of the title compound (LCMS RT= 6.47min,  $MH^+$  255.2)

**$^1H$  NMR (DMSO):** 8.60 (1H, d,  $J$  2.4 Hz), 8.30 (1H, dd,  $J$  9.0 2.4 Hz), 7.95 (1H, d,  $J$  9.0 Hz), 7.43-7.27 (5H, m), 4.44 (2H, s)”

The equivalent reagents which would be used in the above method for the synthesis of 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (compound 1) are 2-amino-4-ethylsulfonylphenol (rather than 2-amino-4-nitrophenol) and 2-naphthoyl chloride (rather than 2-phenylacetyl chloride).

This synthesis teaches the skilled person to purify the product by column chromatography (ethyl acetate/hexanes 1:7 v/v to ethyl acetate/hexanes 1:5 v/v). Such purification provides the compound of formula I in a crystalline impure state consisting mainly of crystalline form II (see below for a definition of this crystalline form).

The drug regulatory authorities are increasingly demanding more information in relation to the polymorphic forms of drug candidates. Consequently, there is a need in the art for processes by which drug candidates can be prepared as a single polymorphic form, and also for novel polymorphic forms of drugs having advantageous properties.

Accordingly, provided are polymorphs of the compound of formula I having advantageous properties and processes by which the polymorphs can be prepared.

In the following description, X-ray powder diffraction pattern peaks are given as  $^{\circ}\text{2}\theta$  and Raman spectra peaks are given as  $\text{cm}^{-1}$ .

In a first embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $14.5\pm0.2$ .

Also in the first embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $16.7\pm0.2$ .

Also in the first embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $19.1\pm0.2$ .

Also in the first embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $24.0\pm0.2$ .

In one aspect of the first embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $14.5\pm0.2$ ,  $16.7\pm0.2$ ,  $19.1\pm0.2$  and  $24.0\pm0.2$ .

In a second embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 2) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $15.9\pm0.2$ ,  $18.5\pm0.2$  and  $23.3\pm0.2$ .

In a third embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 3) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $12.1\pm0.2$ ,  $17.4\pm0.2$ ,  $22.7\pm0.2$ ,  $25.0\pm0.2$  and  $26.5\pm0.2$ .

In a fourth embodiment there is provided a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 4) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $14.6\pm0.2$ ,  $16.1\pm0.2$ ,  $17.0\pm0.2$ ,  $19.3\pm0.2$  and  $29.2\pm0.2$ .

The instant disclosure will now be described with reference to the accompanying drawings in which:

Figure 1 shows the X-ray powder diffraction pattern for polymorphic form 1;

Figure 2 shows the differential scanning calorimetry trace for polymorphic form 1;

5 Figure 3 shows the thermogravimetric analysis trace for polymorphic form 1;

Figure 4 shows the Raman spectra for polymorphic form 1;

Figure 5 shows optical microscope images of polymorphic form 1;

Figure 6 shows the X-ray powder diffraction pattern for polymorphic form 2;

Figure 7 shows the differential scanning calorimetry trace for polymorphic form 2;

10 Figure 8 shows the thermogravimetric analysis trace for polymorphic form 2;

Figure 9 shows the Raman spectra for polymorphic form 2;

Figure 10 shows optical microscope images of polymorphic form 2;

Figure 11 shows the X-ray powder diffraction pattern for polymorphic form 3;

Figure 12 shows the differential scanning calorimetry trace for polymorphic form 3;

15 Figure 13 shows the thermogravimetric analysis trace for polymorphic form 3;

Figure 14 shows the Raman spectra for polymorphic form 3;

Figure 15 shows optical microscope images of polymorphic form 3;

Figure 16 shows the X-ray powder diffraction pattern for polymorphic form 4;

Figure 17 shows the differential scanning calorimetry trace for polymorphic form 4;

20 Figure 18 shows the thermogravimetric analysis trace for polymorphic form 4;

Figure 19 shows the Raman spectra for polymorphic form 4;

Figure 20 shows optical microscope images of polymorphic form 4;

Figure 21 shows a comparison of the X-ray powder diffraction patterns for polymorphic forms 1, 2, 3 and 4;

25 Figure 22 shows a comparison of Raman spectra for polymorphic forms 1, 2, 3 and 4;

Figure 23 shows the X-ray powder diffraction pattern of polymorphic form 1 before and after slurring in methanol;

Figure 24 shows the X-ray powder diffraction pattern of polymorphic form 2 before and after slurring in methanol; and

Figure 25 shows the X-ray powder diffraction pattern of a mixture of polymorphic forms 1, 2 and 3 after slurring in methanol.

5 Figure 26 shows a luciferase reporter assay (murine H2K cells).

Figure 27 shows a dose dependent luciferase induction.

Figure 28 shows an example of TA muscle sections stained with antibody specific for mouse utrophin.

10 Figure 29 shows that mice exposed to CPD-A (V2 and V3) showed increased levels of utrophin expression compared to control.

In one embodiment, provided is the polymorphic form 1 having an X-ray powder diffraction pattern substantially in accordance with figure 1.

In another embodiment, provided is the polymorphic form 1 having a differential scanning calorimetry trace substantially in accordance with figure 2.

15 In another embodiment, provided is the polymorphic form 1 having a thermogravimetric analysis trace substantially in accordance with figure 3.

In another embodiment, provided is the polymorphic form 1 having a Raman spectra substantially in accordance with figure 4.

20 In another embodiment, provided is the polymorphic form 2 having an X-ray powder diffraction pattern substantially in accordance with figure 6.

In another embodiment, provided is the polymorphic form 2 having a differential scanning calorimetry trace substantially in accordance with figure 7.

In another embodiment, provided is the polymorphic form 2 having a thermogravimetric analysis trace substantially in accordance with figure 8.

25 In another embodiment, provided is the polymorphic form 2 having a Raman spectra substantially in accordance with figure 9.

In another embodiment, provided is the polymorphic form 3 having an X-ray powder diffraction pattern substantially in accordance with figure 11.

In another embodiment, provided is the polymorphic form 3 having a differential scanning calorimetry trace substantially in accordance with figure 12.

In another embodiment, provided is the polymorphic form 3 having a thermogravimetric analysis trace substantially in accordance with figure 13.

5 In another embodiment, provided is the polymorphic form 3 having a Raman spectra substantially in accordance with figure 14.

In another embodiment, provided is the polymorphic form 4 having an X-ray powder diffraction pattern substantially in accordance with figure 16.

10 In another embodiment, provided is the polymorphic form 4 having a differential scanning calorimetry trace substantially in accordance with figure 17.

In another embodiment, provided is the polymorphic form 4 having a thermogravimetric analysis trace substantially in accordance with figure 18.

In another embodiment, provided is the polymorphic form 4 having a Raman spectra substantially in accordance with figure 19.

15 In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising greater than 60% of polymorphic form 1, in another embodiment comprising greater than 80% of polymorphic form 1 and in another embodiment greater than 95% of polymorphic form 1.

20 In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising polymorphic form 1 as the only polymorphic form.

25 In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising greater than 60% of polymorphic form 2, in another embodiment comprising greater than 80% of polymorphic form 2 and in another embodiment greater than 95% of polymorphic form 2.

In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising polymorphic form 2 as the only polymorphic form.

30 In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising greater than 60% of

polymorphic form 3, in another embodiment comprising greater than 80% of polymorphic form 3 and in another embodiment greater than 95% of polymorphic form 3.

In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising polymorphic form 3 as the 5 only polymorphic form.

In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising greater than 60% of polymorphic form 4, in another embodiment comprising greater than 80% of polymorphic form 4 and in another embodiment greater than 95% of polymorphic form 4.

10 In one embodiment there is provided a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole having a structure comprising polymorphic form 4 as the only polymorphic form.

Also provided are processes for making each of polymorphic forms 1, 2, 3 and 4.

15 In one embodiment there is provided a process for synthesising polymorphic form 1 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding isopropyl alcohol until a solid product forms wherein the ratio of acetone : isopropyl alcohol is 20 : 80; or

20 dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in ethyl acetate and then adding isopropyl alcohol until a solid product forms wherein the ratio of ethyl acetate : isopropyl alcohol is 40 : 60; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in dimethyl formamide and then adding isopropyl alcohol until a solid product forms wherein the ratio of dimethyl formamide : isopropyl alcohol is 40 : 60; or

25 dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding ethanol until a solid product forms wherein the ratio of acetone : ethanol is 40 : 60; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone at reflux and then allowing the solution to cool to -10 °C to -15 °C until a solid product forms; or

and then

30 (ii) separating the solid product.

In one embodiment there is provided a process for synthesising polymorphic form 2 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding isopropyl alcohol until a solid product forms wherein the ratio of xylene : 5 isopropyl alcohol is either 20 : 80 or 80 : 20;

and then

(ii) separating the solid product.

In one embodiment there is provided a process for synthesising polymorphic form 3 comprising the steps of:

10 (i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding isopropyl alcohol until a solid product forms wherein the ratio of xylene : isopropyl alcohol is 60 : 40;

and then

(ii) separating the solid product.

15 In one embodiment there is provided a process for synthesising polymorphic form 4 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in dimethyl formamide;

and then

20 (ii) removing the dimethyl formamide by evaporation to form a solid product.

The stability of the various solid forms of 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole was investigated by stirring samples of each and mixtures thereof in methanol for defined time periods.

It has been found that polymorphic form 1 exhibits increased stability over previously 25 known forms of 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole. This property of polymorphic form 1 is relevant because it is important that a pharmaceutical product is supplied in a known form. Therefore, if a pharmaceutical is supplied as the most stable polymorph, it may remain in this form as supplied and taken by the patient.

In this regard it has been discovered that polymorphic form 1 retains its structure before and after slurring in methanol for four days at 25°C.

In contrast, after slurring in methanol in a similar manner polymorphic form 2 is converted into polymorphic form 1, and mixtures of polymorphic forms 1, 2 and 3 are also 5 converted into polymorphic form 1.

The polymorphic forms of the compound of formula I for use in the treatment of DMD will generally be administered in the form of a pharmaceutical composition.

Thus, according to a further aspect there is provided a pharmaceutical composition including less than 80% w/w, in another embodiment less than 50% w/w, e.g. 0.1 to 20%, of 10 the polymorphic form of the compound of formula I in admixture with a pharmaceutically acceptable diluent or carrier.

Also provided is a process for the production of such a pharmaceutical composition which comprises mixing the ingredients. Examples of pharmaceutical formulations which may be used, and suitable diluents or carriers, are as follows:

15 for inhalation compositions - coarse lactose;

for tablets, capsules and dragees - microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin;

for suppositories - natural or hardened oils or waxes.

20 The polymorphic form of the compound of formula I in one embodiment is in a form having a mass median diameter of from 0.01 to 10µm. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilisers, e.g. a water-soluble cellulose polymer such as hydroxypropyl methylcellulose, or a water-soluble glycol such as propylene glycol, sweetening and colouring agents and flavourings. Where appropriate, the 25 compositions may be formulated in sustained release form.

The content of the polymorphic form of the compound of formula I in a pharmaceutical composition is generally about 0.01-about 99.9wt%, in one embodiment about 0.1-about 50wt%, relative to the entire preparation.

30 The dose of the polymorphic form of the compound of formula I is determined in consideration of age, body weight, general health condition, diet, administration time,

administration method, clearance rate, combination of drugs, the level of disease for which the patient is under treatment then, and other factors.

While the dose varies depending on the target disease, condition, subject of administration, administration method and the like, for oral administration as a therapeutic agent for the treatment of Duchenne muscular dystrophy in a patient suffering from such a disease is from 0.01 mg - 10 g, in one embodiment 0.1 – 100 mg, is in certain embodiments administered in a single dose or in 2 or 3 portions per day.

The potential activity of the compound of formula I for use in the treatment of DMD may be demonstrated in the following predictive assay and screens.

10 1. Luciferase reporter assay (murine H2K cells)

The cell line used for the screen is an immortalized *mdx* mouse H2K cell line that has been stably transfected with a plasmid containing  $\approx$ 5kb fragment of the Utrophin A promoter including the first untranslated exon linked to a luciferase reporter gene (see Figure 26).

15 Under conditions of low temperature and interferon containing media, the cells remain as myoblasts. These are plated into 96 well plates and cultured in the presence of compound for three days. The level of luciferase is then determined by cell lysis and reading of the light output from the expressed luciferase gene utilising a plate luminometer.

Example of pharmacological dose response of compounds in the assay is shown in  
20 Figure 27.

2. *mdx* mouse

Data obtained from the ADMET data was prioritised and the compounds with the best in vitro luciferase activity and reasonable ADMET data were prioritised for testing in the *mdx* proof of concept study where the outcome was to identify whether any of the compounds had  
25 the ability to increase the levels of utrophin protein in dystrophin deficient muscle when compared to vehicle only dosed control animals.

There were two animals injected with 10mg/kg of compound administered ip daily for  
28 days plus age matched controls. Muscle samples were taken and processed for sectioning (to identify increases in sarcolemmal staining of utrophin) and Western blotting (to identify  
30 overall increases in utrophin levels).

Figure 28 shows an example of TA muscle sections stained with antibody specific for mouse utrophin. Comparison to the *mdx* muscle only injected with vehicle shows an increase in the amount of sarcolemmal bound utrophin.

5 Muscles from the above treated mice were also excised and processed for Western blotting and stained with specific antibodies (see Figure 29). Again using muscle dosed with CPD-A shows a significant increase in the overall levels of utrophin present in both the TA leg muscle and the diaphragm. Both mice exposed to CPD-A (V2 and V3) showed increased levels of utrophin expression compared to control.

10 Positive upregulation data from the first 28 day study were then repeated in a further two mouse 28 day study. A total of three different compounds have shown in duplicate the ability to increase the level of utrophin expression in the *mdx* mouse when delivered daily by ip for 28 days. This data demonstrates the ability of the compound when delivered ip causes a significant increase in the levels of utrophin found in the *mdx* muscle and therefore gives us the confidence that this approach will ameliorate the disease as all the published data to date 15 demonstrates that any increase of utrophin levels over three fold has significant functional effects on dystrophin deficient muscle.

#### The H2K/mdx/Utro A reporter cell line maintenance

The H2K/mdx/Utro A reporter cell line was passaged twice a week until  $\leq 30\%$  confluent. The cells were grown at 33°C in the presence of 10% CO<sub>2</sub>.

20 To remove the myoblasts for plating, they were incubated with Trypsin / EDTA until the monolayer started to detach.

Growth Medium

DMEM Gibco 41966

20% FCS

25 1% Pen/Strep

1% glutamine

10mls Chick embryo extract

Interferon(1276 905 Roche) Add fresh 10 $\mu$ l / 50mls medium

#### Luciferase Assay for 96 Well Plates

The H2K/mdx/Utro A reporter cell line cells were plated out into 96 well plates (Falcon 353296, white opaque) at a density of approximately 5000 cells/well in 190 $\mu$ l normal growth medium. The plates were then incubated at 33°C in the presence of 10% CO<sub>2</sub> for 24 hrs.

5 Compounds were dosed by adding 10 $\mu$ l of diluted compound to each well giving a final concentration of 10 $\mu$ M. The plates were then incubated for a further 48hrs.

Cells were then lysed *in situ* following the manufacture's protocols(Promega Steady-Glo Luciferase Assay System(E2520), then counted for 10 seconds using a plate luminometer (Victor1420).

#### 10 Compound Storage

Compounds for screening were stored at -20°C as 10mM stocks in 100% DMSO until required.

#### Injection of *mdx* mice with compounds

15 Mdx from a breeding colony were selected for testing. Mice were injected daily with either vehicle or up to 50mg/kg of compound using the intreperitoneal route (ip). Mice were weighed and compounds diluted in 5% DMSO, 0.1% tween in PBS.

Mice were sacrificed by cervical dislocation at desired time points, and muscles excised for analysis.

#### Muscle Analysis

#### 20 Immunohistochemistry

Tissues for sectioning were dissected, immersed in OCT (Bright Cryo-M-Bed) and frozen on liquid nitrogen cooled isopentane. Unfixed 8 $\mu$ M cryosections were cut on a Bright Cryostat, and stored at -80°C.

25 In readiness for staining, sections were blocked in 5% fetal calf serum in PBS for 30 mins. The primary antibodies were diluted in blocking reagent and incubated on sections for 1.5 hrs in a humid chamber then washed three times for 5mins in PBS. Secondary antibodies were also diluted in blocking reagent, and incubated for 1 hr in the dark in a humid chamber. Finally sections were washed three times 5mins in PBS and coverslips were mounted with hydromount. Slides were analysed using a Leica fluorescent microscope.

#### 30 Results

Biological activity was assessed using the luciferase reporter assay in murine H2K cells, and is classified as follows:

- + Up to 200% relative to control
- ++ Between 201% and 300% relative to control
- 5        +++ Between 301% and 400% relative to control
- ++++ Above 401% relative to control

5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole	+++
--	-----

### Experimental

10

#### Synthesis of 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole

The following materials were used:

Material	Grade	Moles	Quantity
2-Amino-4-(ethylsulfonyl)phenol	97%	4.72 mol	948 g
2-Naphthoyl chloride	98 %	4.72 mol	900 g
Methanesulfonic acid	98 %	2.36 mol	153 mL
Xylenes mixed	96 %	n/a	6 L
Sodium hydroxide	-	9.44 mol	378 g
tert-Butyl methyl ether	99 %	-	1.0 L

#### Procedure:

15        A vessel was equipped with a retreat blade stirrer and downward pumping turbine, a five necked flange lid, seal and clamp, stirrer gland and overhead stirrer, thermometer pocket, Dean-Stark trap, dropping funnel and condenser. The water to the condenser was then switched on.

20        The sodium hydroxide and 0.80 L of water were then mixed (whilst cooling in an ice bath until all the sodium hydroxide has dissolved - caution exothermic). The resulting solution was then transferred to a scrubber appropriately attached to the vessel.

The 2-amino-4-(ethylsulfonyl)phenol and 2.00 L of xylenes (mixed) were then transferred to the vessel, and the reagents and solvent were stirred at 100 rpm.

Then, the 2-naphtholyl chloride was dissolved in 2.00 L of xylenes (mixed) and transferred into the vessel. The stirring rate was increased to 150 rpm.

5 The temperature of the solution was gradually increased to 100°C over a period of not less than 30 mins, and then maintained at that level for 10 mins. (Caution: HCl gas is evolved during this process through the gas scrubber). The stirrer speed was then increased to 315 rpm and the temperature gradually increased over a period of 30 minutes until reflux (155°C) at which level it was maintained for 90 mins. (Caution: HCl gas is evolved during this 10 process through the gas scrubber).

The methanesulfonic acid was then added drop-wise over a period of 30 mins and reflux was maintained until no further water was being collected in the Dean-Stark apparatus (approx 15 mins).

15 The heat was then removed and the pipe adapter from the Dean-Stark apparatus disconnected. The resulting solution was allowed to cool to 90°C, and then filtered using Whatman 1 filter paper.

The resulting solution was then left at ambient temperature for 18h, after which time the product crystallised, and the product was separated by filtration using Whatman 1 filter paper. The product was then washed with 1× 1.0 L of tert-butyl methyl ether (TBME)

20 The product was then dried in a vacuum oven at 65°C at a pressure of 10mbar until constant weight was achieved (less than 0.5 g difference between consecutive measurements of mass which must be at least 1 h apart).

The product was obtained as a sandy-beige powder in a yield of 80%.

25 Characterisation:

**5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole**

LCMS RT= 6.94min, MH<sup>+</sup> 338.1;

<sup>1</sup>H NMR (DMSO): 8.90 (1H, br), 8.34 (1H, d, *J* 1.4 Hz), 8.30 (1H, dd, *J* 8.6 1.7 Hz), 8.24-8.05 (4H, m), 7.99 (1H, dd, *J* 8.5 1.8 Hz), 7.73-7.64 (2H, m), 3.41 (2H, q, *J* 7.3 Hz), 1.15 (3H, t, *J* 7.3 Hz);

MP = 160-161°C.

### Synthesis of polymorphic forms

5 1. Procedure

100 mg of the compound of formula I was dissolved in the minimum amount of good solvent and then the anti-solvent was added to induce crystallisation. The supernatant liquor was then removed, and the resulting solid was dried under vacuum for 12 hrs.

10 2. Thermodynamic stability testing

Slurrying Experiment (single form)

Approximately 10 mg of two polymorphic forms was slurried in 0.25ml of methanol for 4 days at either room temperature or 60 °C. The supernatant liquor was then removed and the resulting solid was dried under vacuum for 24 hrs.

15

Slurrying Experiment (mixed forms)

Approximately 10 mg of a mixture of polymorphic forms were slurried together in 0.25ml of methanol for 1 day at either room temperature or 60°C. The supernatant was then removed via syringe and the resulting solid was dried under vacuum for 24 hrs and analysed by 20 powder X-ray diffraction.

3. Analytical techniques

3.1 X-Ray Powder Diffraction (XRPD)

Approximately 2 mg of sample was gently compressed on the XRPD zero back ground single 25 obliquely cut silica sample holder. The sample was then loaded into a Philips X-Pert MPD diffractometer and analysed using the following experimental conditions:

Tube anode: Cu

Generator tension: 40 kV

30 Tube current: 40 mA

Wavelength alpha1: 1.5406 Å

Wavelength alpha2: 1.5444 Å

Start angle [2θ]: 5

End angle [2θ]: 35

Time per step: 2.5 seconds

5 Scan step size: 0.06

### 3.2 Differential Scanning Calorimetry

Approximately 2 mg of sample was weighed into an aluminium DSC pan and sealed using a non-hermetic lid. The sample was then loaded into a Perkin-Elmer Diamond DSC (equipped 10 with a liquid nitrogen cooling unit) cooled and held at 0°C. Once a stable heat-flow response was seen, the sample was then heated from 0 to 200°C at scan rate of 200°C/min and the resulting heat flow response was monitored. A 20 ml/min helium purge was used to prevent thermally induced oxidation of the sample during heating and also to reduce the thermal lag 15 through the sample to increase the instrument sensitivity. Prior to analysis, the instrument was temperature and heat-flow calibrated using an indium reference standard.

### 3.3 Gravimetric Vapour Sorption

Approximately 15 mg of sample was placed into a wire-mesh vapour sorption balance pan and loaded into an 'IgaSorp' vapour sorption balance (Hiden Analytical Instruments). The 20 sample was then dried by maintaining a 0 % humidity environment until no further weight change was recorded. Subsequently, the sample was then subjected to a ramping profile from 0 – 90 % RH at 10 % RH increments, maintaining the sample at each step until equilibration had been attained (99.5 % step completion). Upon reaching equilibration, the % RH within 25 the apparatus was ramped to the next step and the equilibration procedure repeated. After completion of the sorption cycle, the sample was then dried using the same procedure. The weight change during the sorption/desorption cycles were then monitored, allowing for the hygroscopic nature of the sample to be determined.

### 3.4 Thermogravimetic Analysis

30 Approximately 5 mg of sample was accurately weighed into a platinum TGA pan and loaded into a TGA 7 gravimetric analyser held at room temperature. The sample was then heated at a rate of 10°C/min from 20°C to 250°C during which time the change in weight monitored. The purge gas used was nitrogen at a flow rate of 20 ml/min. Prior to analysis the instrument

was weight calibrated using a 100 mg reference weight and temperature calibrated using an alumel reference standard.

## Results

5

### Polymorphic form 1

Polymorphic form 1 was prepared under the above conditions using following solvent combinations:

<u>Good solvent</u>	<u>Anti-solvent</u>	<u>Ratio good solvent : anti-solvent</u>
Acetone	isopropyl alcohol	20 : 80
ethyl acetate	isopropyl alcohol	40 : 60
dimethyl formamide	isopropyl alcohol	40 : 60
Acetone	ethanol	40 : 60

10

Polymorphic form 1 gives an X-ray powder diffraction pattern according to figure 1 having the following peaks:

	<u>No.</u>	<u>Position. [°2Th.]</u>	<u>d-spacing [Å]</u>	<u>Relative Intensity [%]</u>
15	1	8.74041	0.11722	7.71
	2	12.2445	7.22867	9.15
	3	14.5128	6.10355	24.14
	4	15.3453	5.77424	100.00
	5	16.7016	5.30825	13.43
20	6	17.5358	5.05758	9.16
	7	17.9991	4.92841	11.13
	8	19.0954	4.64787	24.44
	9	19.5539	4.53993	15.30
	10	19.9900	4.44185	12.98
25	11	20.7114	4.28873	19.80
	12	20.9551	4.23941	17.18
	13	22.3866	3.97145	12.06
	14	24.0108	3.70636	14.53
	15	24.4808	3.63626	12.09
30	16	25.8892	3.44154	82.90
	17	26.6900	3.34008	7.88

18	27.4500	3.24931	2.61
19	28.8546	3.09425	12.72
20	29.5922	3.01878	13.84
21	30.4300	2.93755	2.95
5	22 31.4100	2.84810	11.94
	23 33.2507	2.69453	8.11
	24 35.5350	2.52638	6.65
	25 36.5096	2.46115	5.22
	26 37.2500	2.41391	3.19
10	27 38.6897	2.32734	5.22
	28 40.1100	2.24814	6.16
	29 42.4100	2.13139	2.71
	30 43.6241	2.07485	5.81
	31 45.0900	2.01074	5.28
15	32 45.7704	1.98242	7.23

Polymorphic form 1 gives a differential scanning calorimetry trace according to figure 2.

Polymorphic form 1 gives a thermogravimetric analysis trace according to figure 3.

Polymorphic form 1 gives a Raman spectra according to figure 4 having the following peaks:

20 No. Position. [cm<sup>-1</sup>]

1	1628.57
2	1611.21
3	1554.92
4	1508.12
25	5 1463.63
	6 1429.89
	7 1390.53
	8 1362.14
	9 1264.03
30	10 1237.83
	11 1190.93
	12 921.63

Figure 5 shows optical microscope images of polymorphic form 1.

35 Polymorphic form 2

Polymorphic form 2 was prepared under the above conditions using following solvent combinations:

<u>Good solvent</u>	<u>Anti-solvent</u>	<u>Ratio good solvent : anti-solvent</u>
Xylene	isopropyl alcohol	20 : 80
Xylene	isopropyl	80 : 200

	alcohol	
--	---------	--

Polymorphic form 2 gives an X-ray powder diffraction pattern according to figure 6 having the following peaks:

5	No.	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
1	1	9.3400	9.46903	10.85
2	2	12.6400	7.00334	0.70
3	3	13.8911	6.37529	14.17
4	4	14.4657	6.12329	39.26
10	5	15.0183	5.89922	27.06
6	6	15.1577	5.84528	30.73
7	7	15.2469	5.81130	29.86
8	8	15.9393	5.56038	41.58
9	9	16.8200	5.27116	44.97
15	10	17.0323	5.20594	43.47
11	11	17.8573	4.96725	34.13
12	12	18.5128	4.79281	55.26
13	13	19.2033	4.62200	27.93
14	14	20.0240	4.43439	33.44
20	15	20.6864	4.29386	12.85
16	16	20.7079	4.28945	13.81
17	17	22.3479	3.97824	46.15
18	18	23.3108	3.81605	85.94
19	19	24.3157	3.66057	16.97
25	20	25.6110	3.47830	100.00
21	21	26.0183	3.42476	28.61
22	22	27.4530	3.24896	17.17
23	23	27.9900	3.18783	15.37
24	24	28.0908	3.17663	13.56
30	25	28.9336	3.08599	29.83
26	26	30.0254	2.97621	23.50
27	27	30.8547	2.89808	17.04
28	28	34.4400	2.60415	3.48
29	29	36.4900	2.46242	13.97
35	30	38.7300	2.32501	5.56
31	31	40.6400	2.22004	26.93
32	32	44.4475	2.03831	17.17
33	33	45.6477	1.98747	22.08
34	34	47.6607	1.90812	18.98

40

Polymorphic form 2 gives a differential scanning calorimetry trace according to figure 7.

Polymorphic form 2 gives a thermogravimetric analysis trace according to figure 8.

Polymorphic form 2 gives a Raman spectra according to figure 9 having the following peaks:

<u>No.</u>	<u>Position. [cm<sup>-1</sup>]</u>
1	1630.74
2	1611.54
3	1557.07
5	1507.80
5	1426.48
6	1393.55
7	1262.55
8	1237.64
10	918.36

Figure 10 shows optical microscope images of polymorphic form 2.

### Polymorphic form 3

15 Polymorphic form 3 was prepared under the above conditions using following solvent combination:

<u>Good solvent</u>	<u>Anti-solvent</u>	<u>Ratio good solvent : anti-solvent</u>
Xylene	isopropyl alcohol	60 : 40

20 Polymorphic form 3 gives an X-ray powder diffraction pattern according to figure 11 having the following peaks:

<u>No.</u>	<u>Pos. [°2Th.]</u>	<u>d-spacing [Å]</u>	<u>Rel. Int. [%]</u>
1	12.1430	7.28886	25.01
2	12.7134	6.96307	6.44
3	13.6600	6.48261	8.31
25	4 15.5495	5.69886	100.00
5	16.0600	5.51885	2.13
6	16.8040	5.27613	18.64
7	17.3537	5.11022	41.67
8	18.3400	4.83758	2.60
30	9 18.3943	4.82343	8.31
10	19.6000	4.52934	2.13
11	20.2870	4.37749	5.54
12	22.0370	4.03365	9.85
35	13 22.7100	3.91562	19.37
14	24.9757	3.56531	29.27
15	25.6058	3.47899	35.69
16	26.5134	3.36193	19.69
17	27.4021	3.25488	36.92
18	27.7695	3.21264	32.38
40	19 28.2812	3.15567	13.54
20	29.0800	3.07078	3.31

Polymorphic form 3 gives a differential scanning calorimetry trace according to figure 12.

Polymorphic form 3 gives a thermogravimetric analysis trace according to figure 13.

Polymorphic form 3 gives a Raman spectra according to figure 14 having the following peaks:

	<u>No.</u>	<u>Position. [cm<sup>-1</sup>]</u>
5	1	1632.78
	2	1613.30
	3	1546.09
	4	1456.03
10	5	1426.77
	6	1390.81
	7	1346.25
	8	1261.88
	9	1239.12
15	10	1190.05
	11	1157.98
	12	1121.54
	13	955.92
	14	929.81
20	15	860.57

Figure 15 shows optical microscope images of polymorphic form 3.

#### Polymorphic form 4

25 Polymorphic form 4 was prepared by dissolving 100 mg of the compound of formula I in dimethyl formamide and then removing the solvent by evaporation.

<u>Good solvent</u>	<u>Anti-solvent</u>	<u>Ratio good solvent : anti-solvent</u>
dimethyl formamide	-	-

30 Polymorphic form 4 gives an X-ray powder diffraction pattern according to figure 16 having the following peaks:

	<u>No.</u>	<u>Pos. [°2Th.]</u>	<u>d-spacing [Å]</u>	<u>Rel. Int. [%]</u>
35	1	12.4100	7.13262	2.58
	2	14.6200	6.05903	46.05
	3	15.2274	5.81868	76.40
	4	16.0989	5.50562	29.99
	5	16.9513	5.23064	35.06
	6	18.0105	4.92534	20.11
	7	18.6225	4.76483	15.15

8	19.2734	4.60535	22.30
9	20.1430	4.40845	28.54
1	0 20.6800	4.29518	24.48
11	22.4554	3.95944	17.33
5	12 23.4994	3.78585	13.79
	13 23.8598	3.72947	16.11
	14 24.4279	3.64400	27.84
	15 25.8355	3.44858	100.00
	16 29.1864	3.05982	35.71
10	17 30.9869	2.88602	14.70
	18 34.1490	2.62567	11.86
	19 35.4100	2.53501	6.05
	20 38.5794	2.33374	12.20
	21 40.8300	2.21014	13.16
15	22 43.7100	2.07097	7.24
	23 45.7500	1.98326	16.51
	24 47.8854	1.89969	15.10
	25 48.6259	1.87248	13.89

Polymorphic form 4 gives a differential scanning calorimetry trace according to figure 17.

20 Polymorphic form 4 gives a thermogravimetric analysis trace according to figure 18.

Polymorphic form 4 gives a Raman spectra according to figure 19 having the following peaks:

	<u>No.</u>	<u>Position. [cm<sup>-1</sup>]</u>
25	1	1611.74
	2	1556.66
	3	1505.46
	4	1455.21
	5	1426.26
	6	1390.80
30	7	1344.56
	8	1238.72
	9	1187.49
	10	1119.38
	11	1061.06
35	12	916.21

Figure 20 shows optical microscope images of polymorphic form 4.

Slurrying Experiments

## 1. Polymorphic form 1

5 Polymorphic form 1 was slurried in methanol and then the solid product isolated using the above slurring experiment (single form). The X-ray powder diffraction pattern of the solid product was obtained. The experiment was performed twice and the resulting diffraction patterns are illustrated by figure 23. It can be seen that the diffraction pattern is the same before and after slurring indicating that there is no change in the polymorphic form.

## 10 2. Polymorphic form 2

Polymorphic form 2 was slurried in methanol and then the solid product isolated using the above slurring experiment (single form). The X-ray powder diffraction pattern of the solid product was obtained. The experiment was performed twice and the resulting diffraction patterns are illustrated by figure 24 together with the diffraction pattern for polymorphic form 15 1. It can be seen that the diffraction pattern of the product subsequent to slurring is the same as that for polymorphic form 1, indicating that subsequent to slurring, polymorphic form 1 has converted to polymorphic form 2.

## 3. Mixed polymorphic forms 1, 2 and 3.

20 The following mixtures of polymorphic forms were slurried in methanol according to the above slurring experiment (mixed forms) both at 60°C and at 25°C:

Forms 1 and 2

Forms 1 and 3

25 Forms 2 and 3

The X-ray powder diffraction pattern of the solid products after slurring were obtained. The spectra are illustrated by figure 25.

30 As can be seen, at 25°C, after slurring all mixtures converted into polymorphic form 1. However, after slurring at 60°C the spectra indicate only partial conversion into polymorphic form 1, indicating that the free energy difference between the polymorphic forms may be more finely balanced at 60°C rather than at 25°C.

**WHAT IS CLAIMED IS:**

1. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $14.5\pm0.2$ .
2. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $16.7\pm0.2$ .
3. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $19.1\pm0.2$ .
4. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising a peak at  $24.0\pm0.2$ .
- 15 5. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 1) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $14.5\pm0.2$ ,  $16.7\pm0.2$ ,  $19.1\pm0.2$  and  $24.0\pm0.2$ .
6. A polymorphic form according to any of claims 1 to 5 having an X-ray powder diffraction pattern substantially in accordance with figure 1.
- 20 7. A polymorphic form according to any of claims 1 to 6 having a differential scanning calorimetry trace substantially in accordance with figure 2.
8. A polymorphic form according to any of claims 1 to 7 having a thermogravimetric analysis trace substantially in accordance with figure 3.
9. A polymorphic form according to any of claims 1 to 8 having a Raman spectra substantially in accordance with figure 4.
- 25 10. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising greater than 60% of a polymorphic form according to any of claims 1 to 9.

11. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising a polymorphic form according to any of claims 1 to 9 as the only polymorphic form.
- 5 12. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 2) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $15.9\pm0.2$ ,  $18.5\pm0.2$  and  $23.3\pm0.2$ .
13. A polymorphic form according to claim 12 having an X-ray powder diffraction pattern substantially in accordance with figure 6.
- 10 14. A polymorphic form according to claim 12 or 13 having a differential scanning calorimetry trace substantially in accordance with figure 7.
15. A polymorphic form according to any of claims 12 to 14 having a thermogravimetric analysis trace substantially in accordance with figure 8.
16. A polymorphic form according to any of claims 12 to 15 having a Raman spectra substantially in accordance with figure 9.
- 15 17. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising greater than 60% of a polymorphic form according to any of claims 12 to 16.
- 20 18. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising a polymorphic form according to any of claims 12 to 16 as the only polymorphic form.
- 25 19. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 3) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at  $12.1\pm0.2$ ,  $17.4\pm0.2$ ,  $22.7\pm0.2$ ,  $25.0\pm0.2$  and  $26.5\pm0.2$ .
20. A polymorphic form according to claim 19 having an X-ray powder diffraction pattern substantially in accordance with figure 11.
- 30 21. A polymorphic form according to claim 19 or 20 having a differential scanning calorimetry trace substantially in accordance with figure 12.

22. A polymorphic form according to any of claims 19 to 21 having a thermogravimetric analysis trace substantially in accordance with figure 13.
23. A polymorphic form according to any of claims 19 to 22 having a Raman spectra substantially in accordance with figure 14.
- 5 24. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising greater than 60% of a polymorphic form according to any of claims 19 to 23.
- 10 25. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising a polymorphic form according to any of claims 19 to 23 as the only polymorphic form.
- 15 26. A polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (polymorphic form 4) characterised in that it provides an X-ray powder diffraction pattern comprising peaks at 14.6±0.2, 16.1±0.2, 17.0±0.2, 19.3±0.2 and 29.2±0.2
27. A polymorphic form according to claim 26 having an X-ray powder diffraction pattern substantially in accordance with figure 16.
28. A polymorphic form according to claim 26 or 27 having a differential scanning calorimetry trace substantially in accordance with figure 17.
- 20 29. A polymorphic form according to any of claims 26 to 28 having a thermogravimetric analysis trace substantially in accordance with figure 18.
30. A polymorphic form according to any of claims 26 to 29 having a Raman spectra substantially in accordance with figure 19.
- 25 31. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising greater than 60% of a polymorphic form according to any of claims 26 to 30.
- 30 32. A pharmaceutical composition comprising a compound of the formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole, wherein the compound of formula 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole has a structure comprising a polymorphic form according to any of claims 26 to 30 as the only polymorphic form.

33. A process for synthesising a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole according to any of claims 1 to 9 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding isopropyl alcohol until a solid product forms wherein the ratio of acetone :

5 isopropyl alcohol is 20 : 80; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in ethyl acetate and then adding isopropyl alcohol until a solid product forms wherein the ratio of ethyl acetate : isopropyl alcohol is 40 : 60; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in dimethyl 10 formamide and then adding isopropyl alcohol until a solid product forms wherein the ratio of dimethyl formamide : isopropyl alcohol is 40 : 60; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding ethanol until a solid product forms wherein the ratio of acetone : ethanol is 40 : 60; or

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone at reflux 15 and then cooling to -10 °C to -15 °C until a solid product forms;

and then

(ii) separating the solid product.

34. A process for synthesising a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole according to any of claims 12 to 16 comprising the steps 20 of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding isopropyl alcohol until a solid product forms wherein the ratio of xylene : isopropyl alcohol is either 20 : 80 or 80 : 20;

and then

25 (ii) separating the solid product.

35. A process for synthesising a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole according to any of claims 19 to 23 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding isopropyl alcohol until a solid product forms wherein the ratio of xylene : isopropyl alcohol is 60 : 40;

and then

5 (ii) separating the solid product.

36. A process for synthesising a polymorphic form of the compound 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole according to any of claims 26 to 30 comprising the steps of:

(i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in dimethyl  
10 formamide;

and then

(ii) removing the dimethyl formamide by evaporation to form a solid product.

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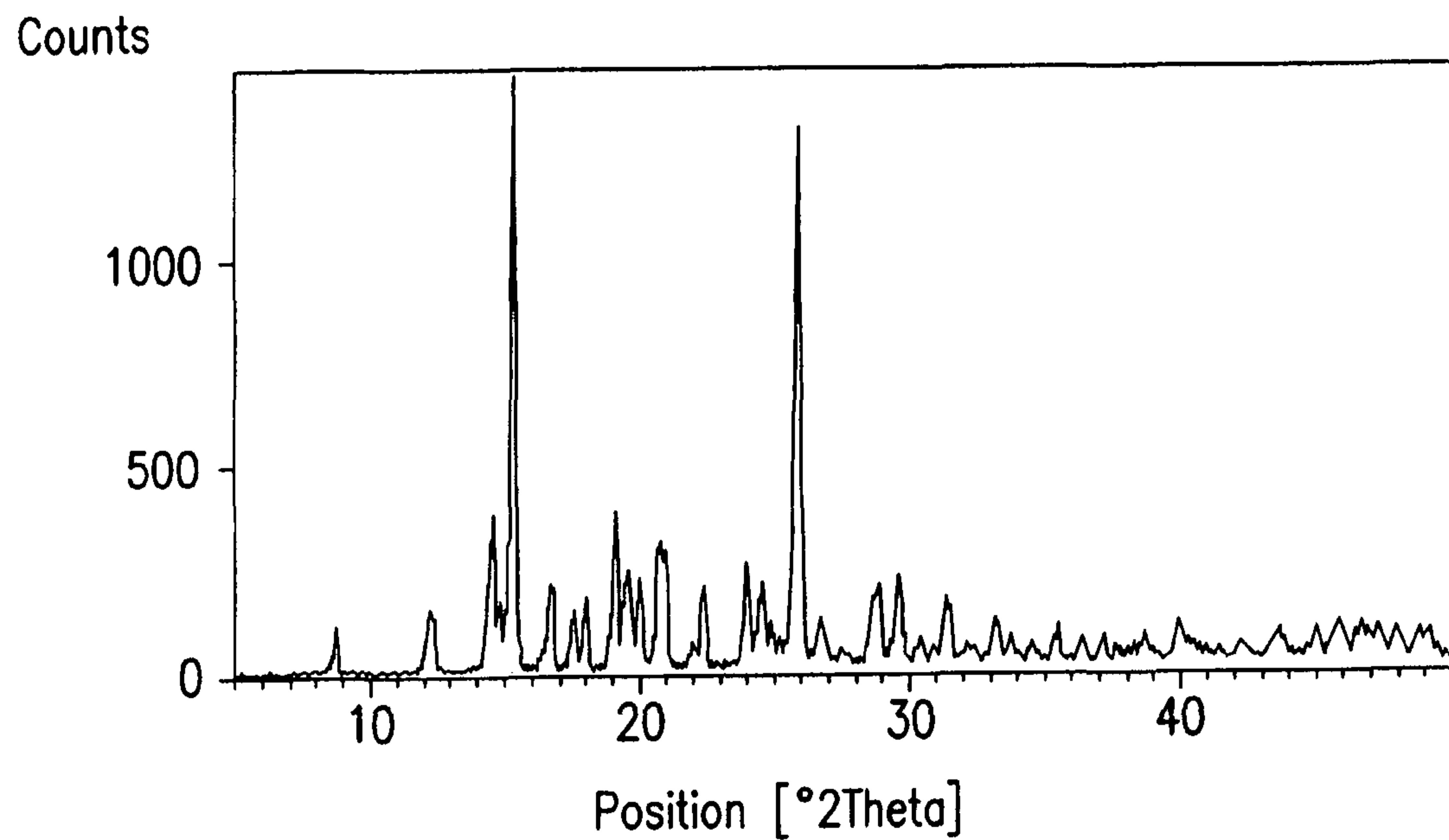


FIG. 1

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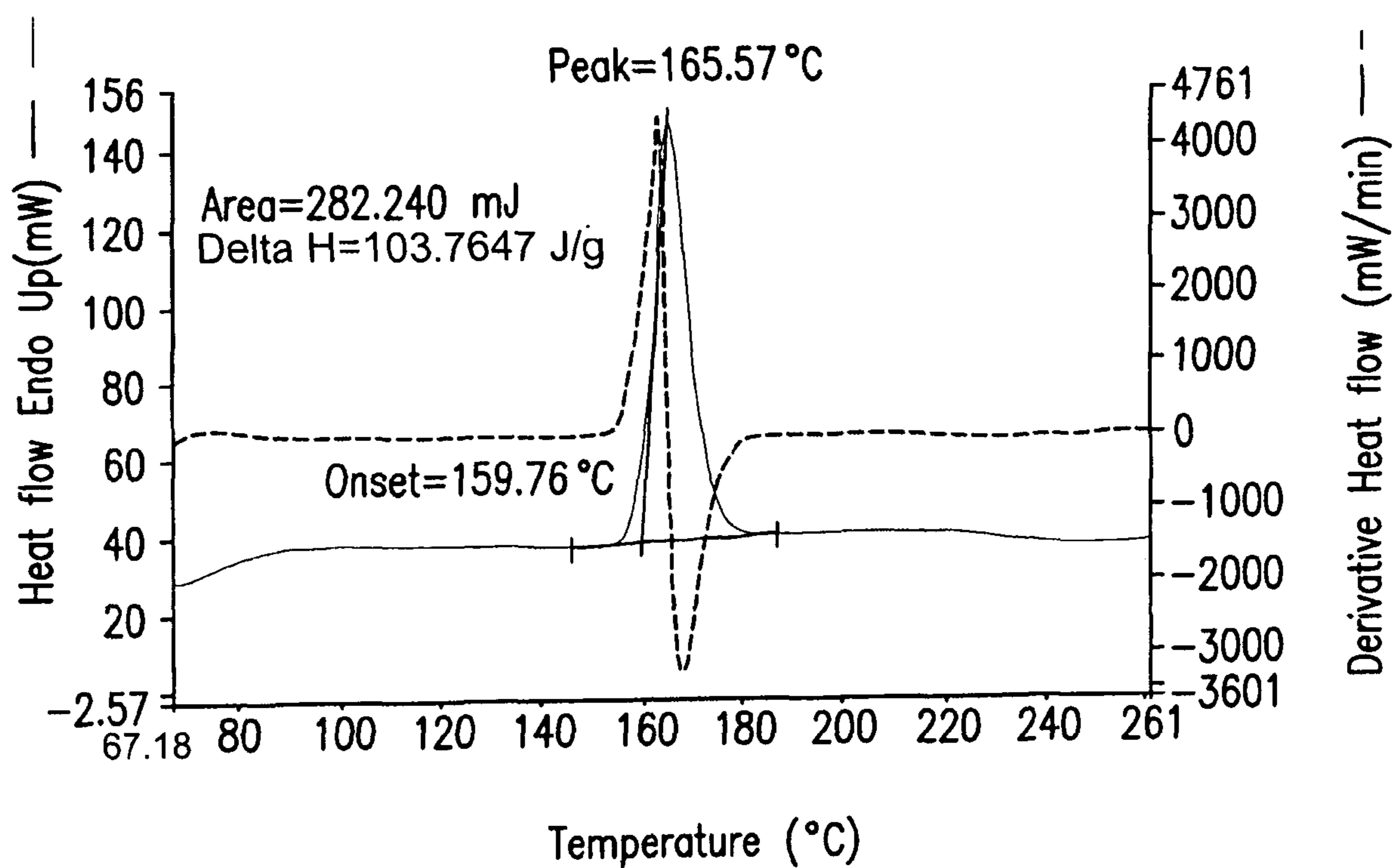


FIG.2

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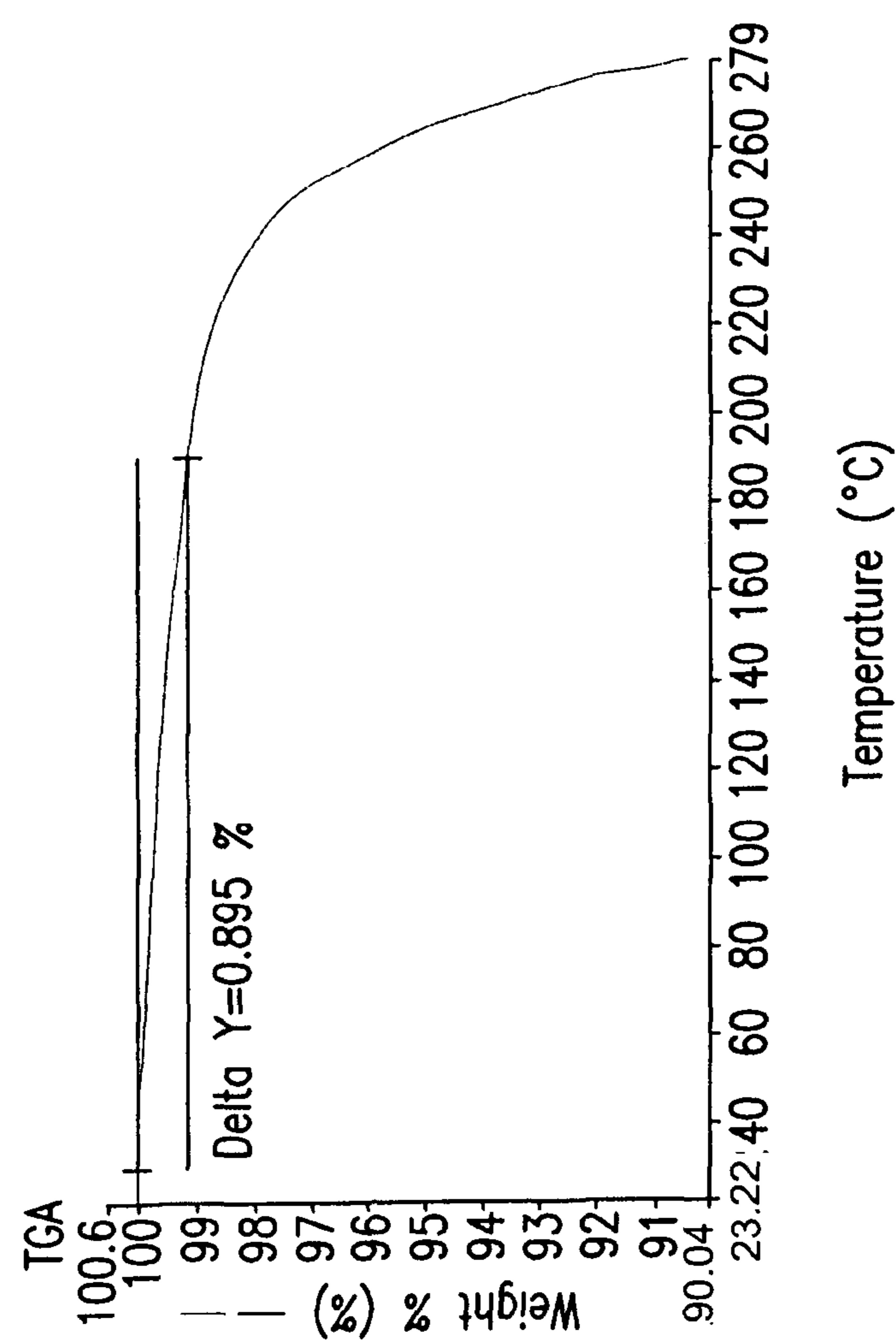


FIG.3

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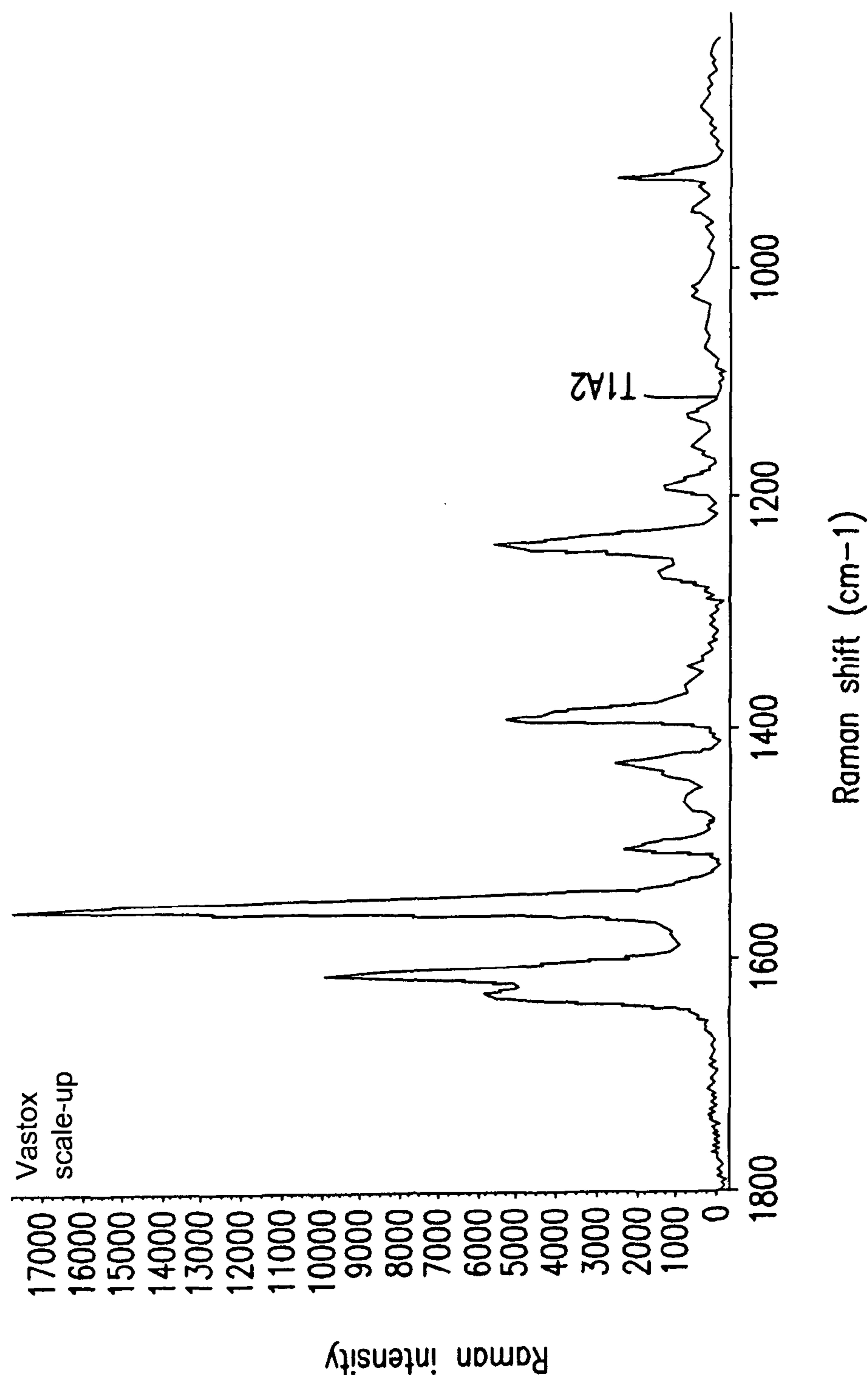


FIG. 4

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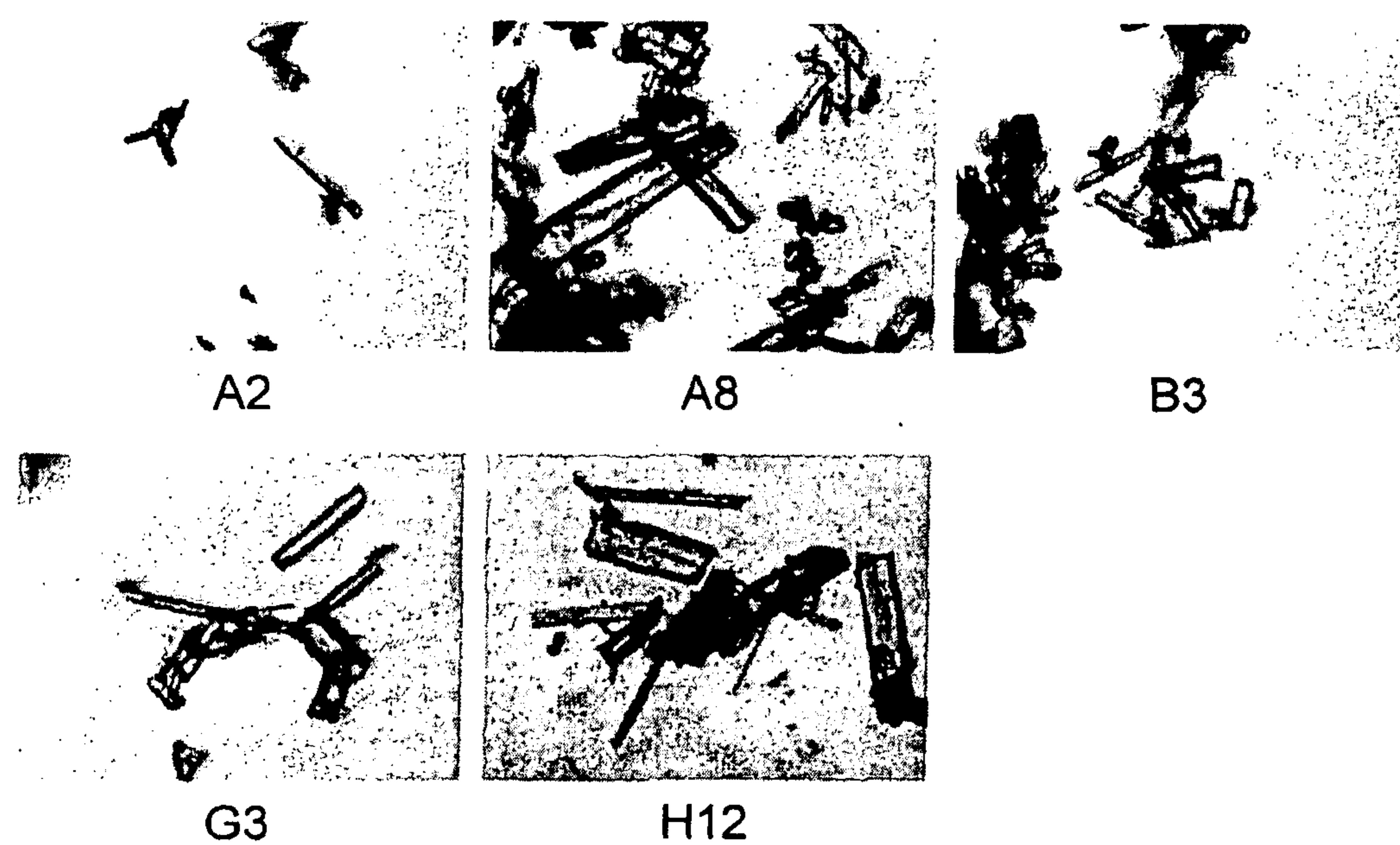


FIG.5

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Counts

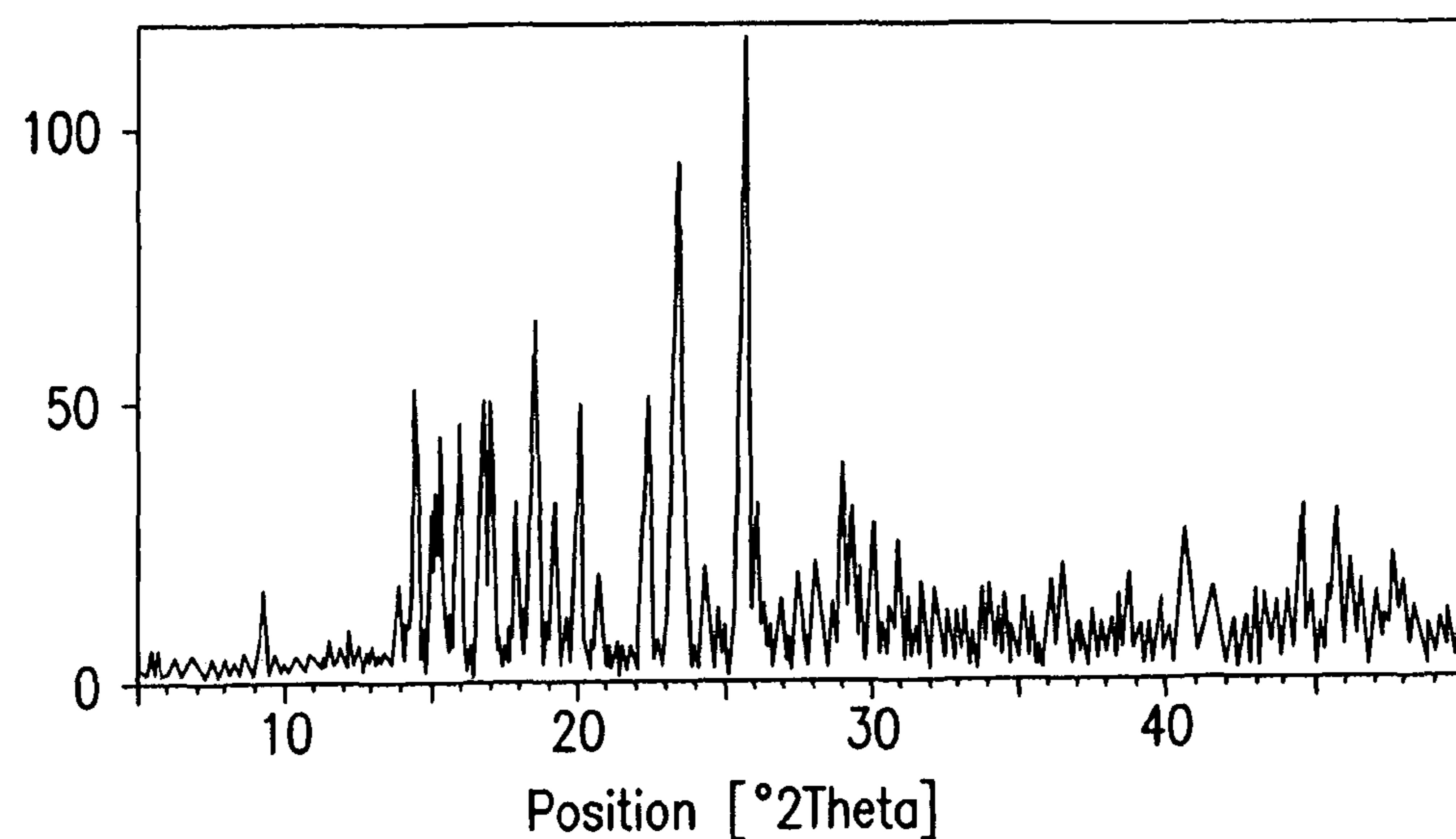


FIG.6

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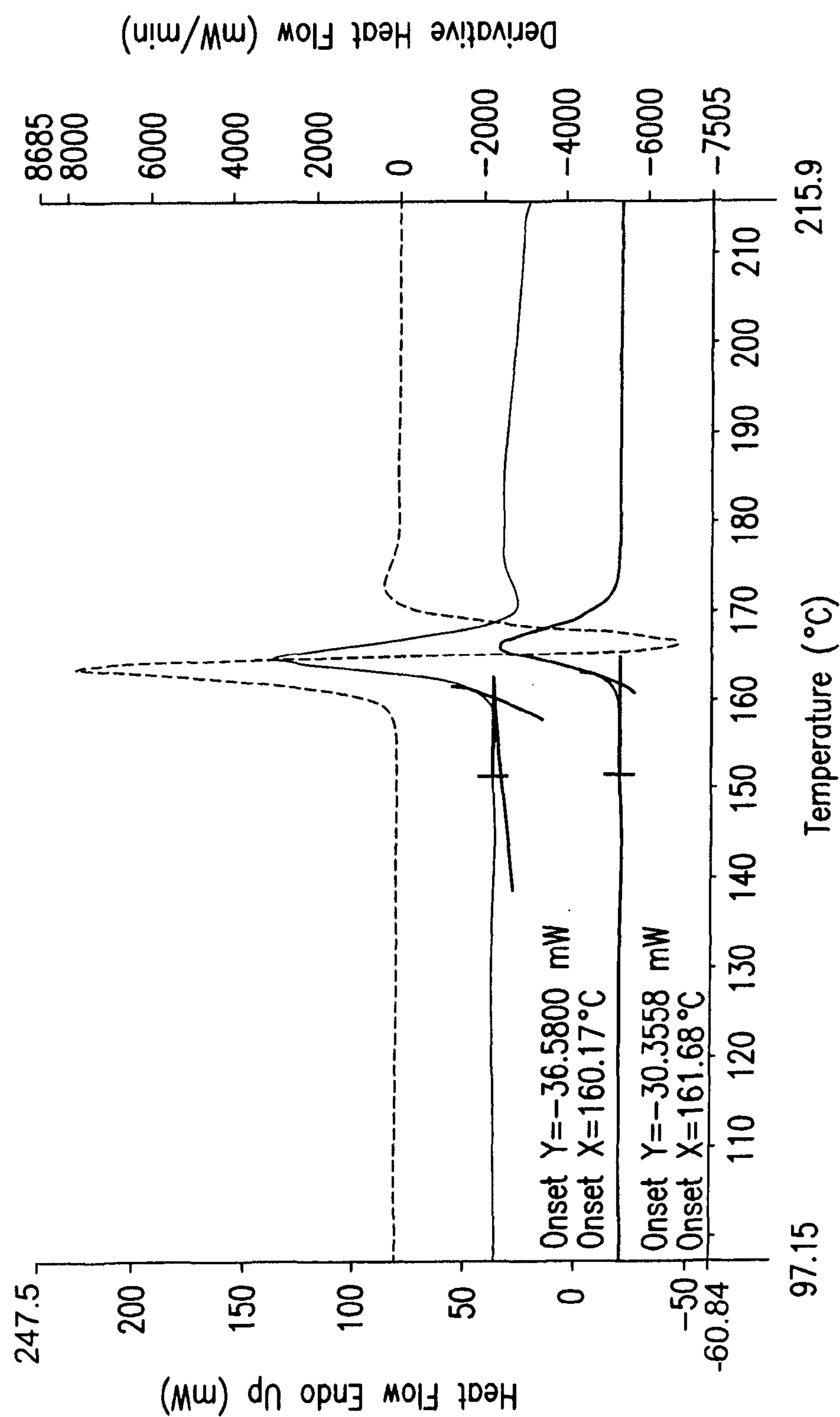


FIG. 7

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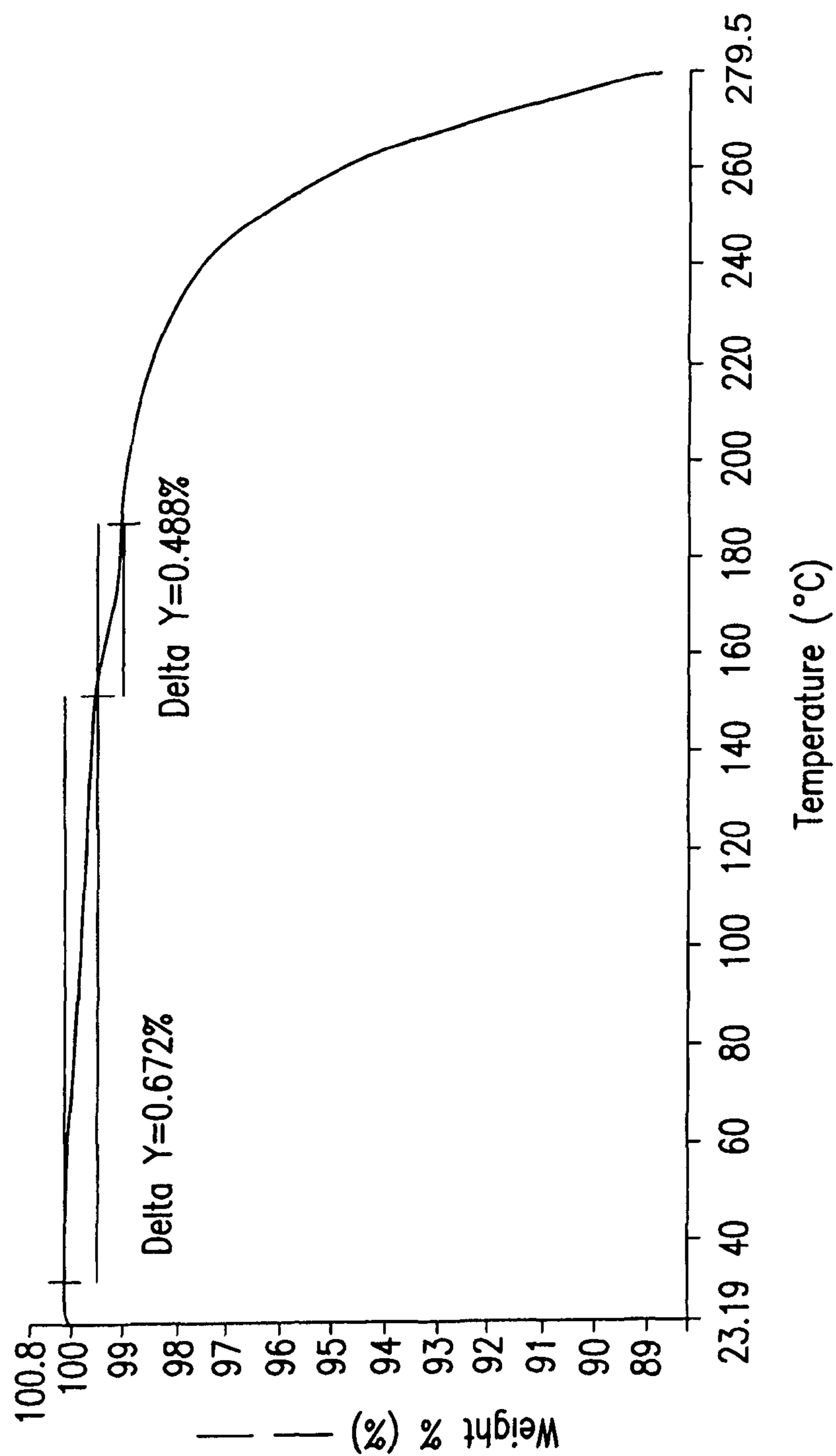


FIG. 8

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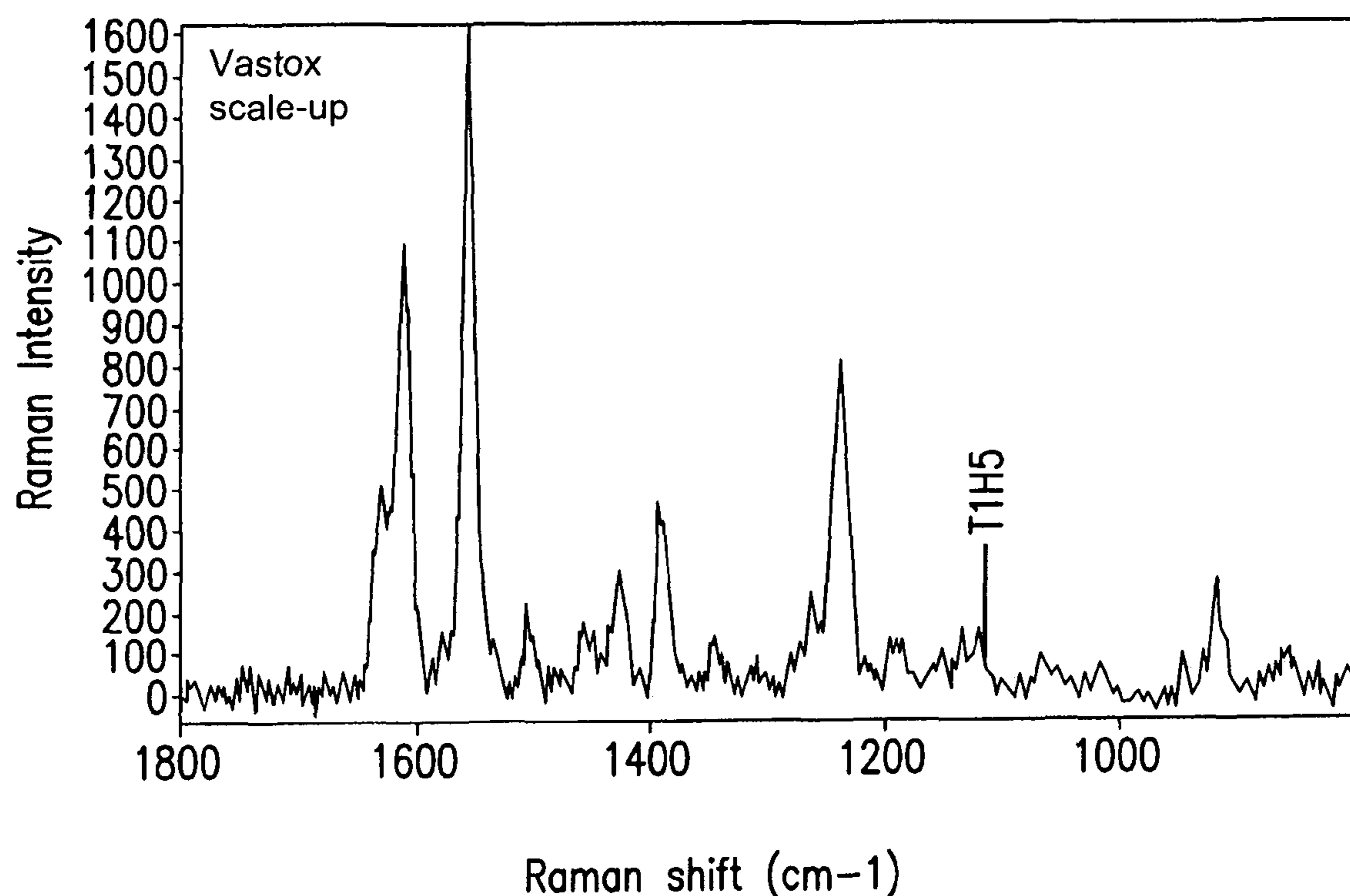


FIG.9

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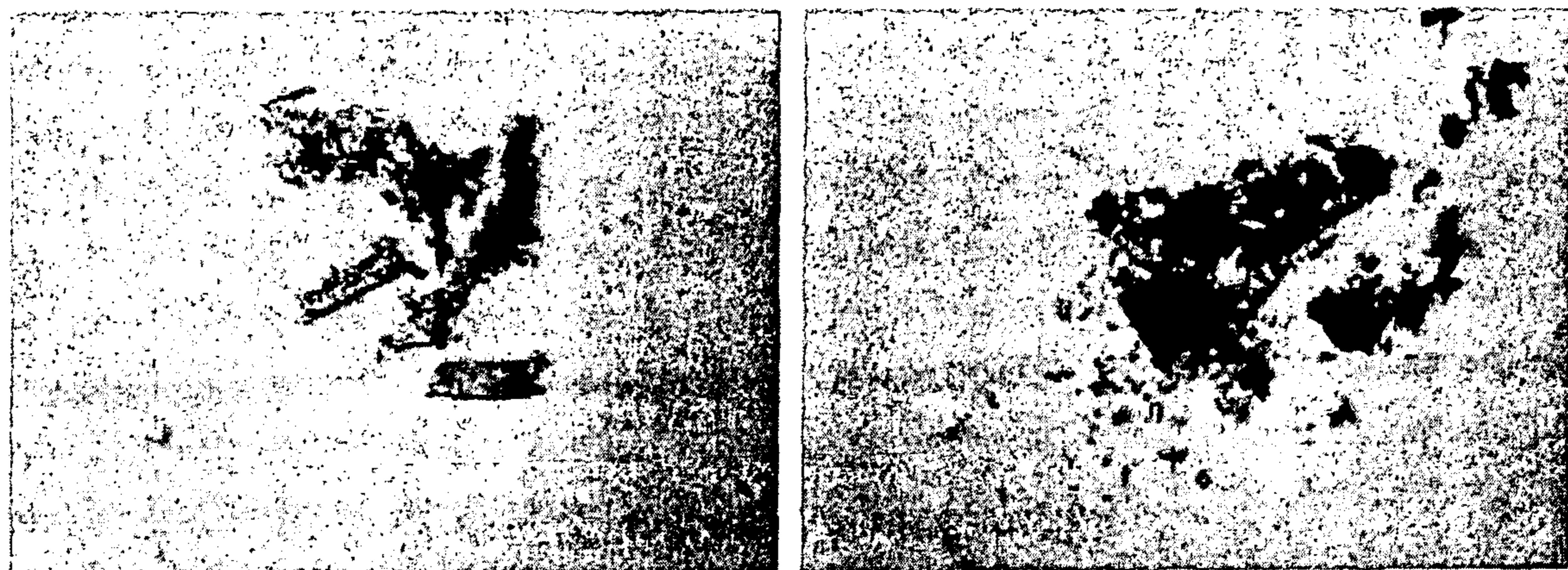


FIG.10

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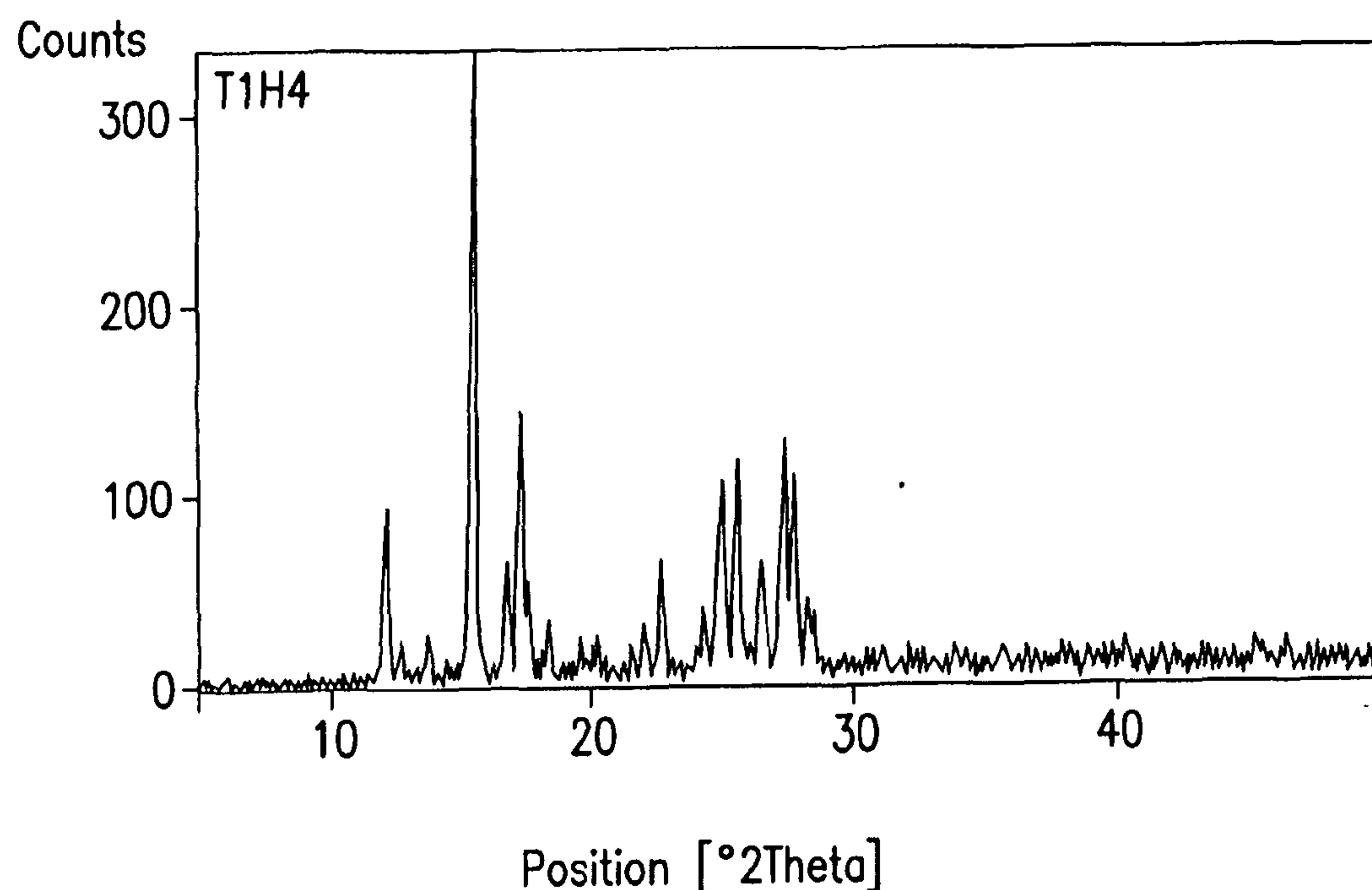


FIG. 11

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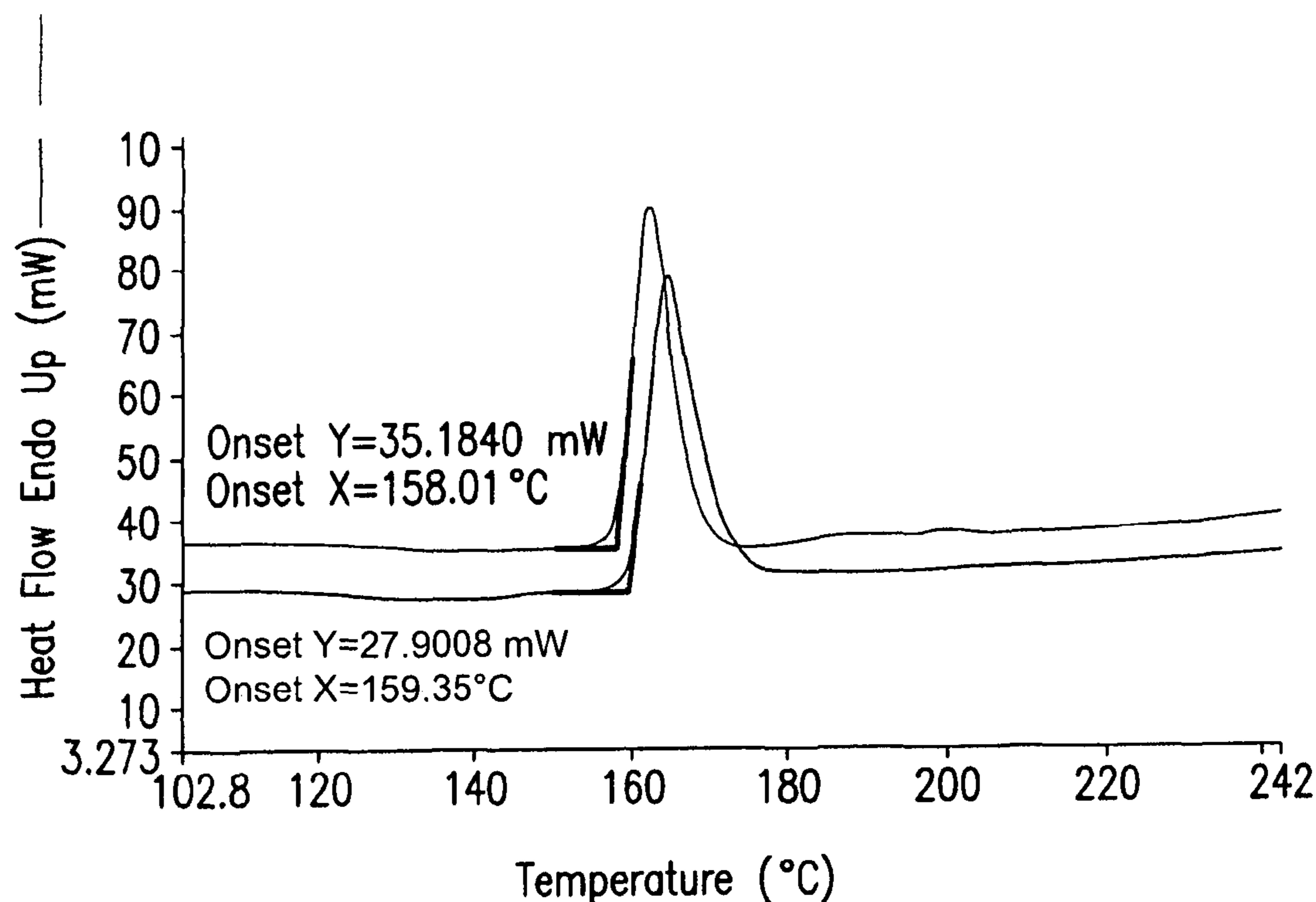


FIG. 12

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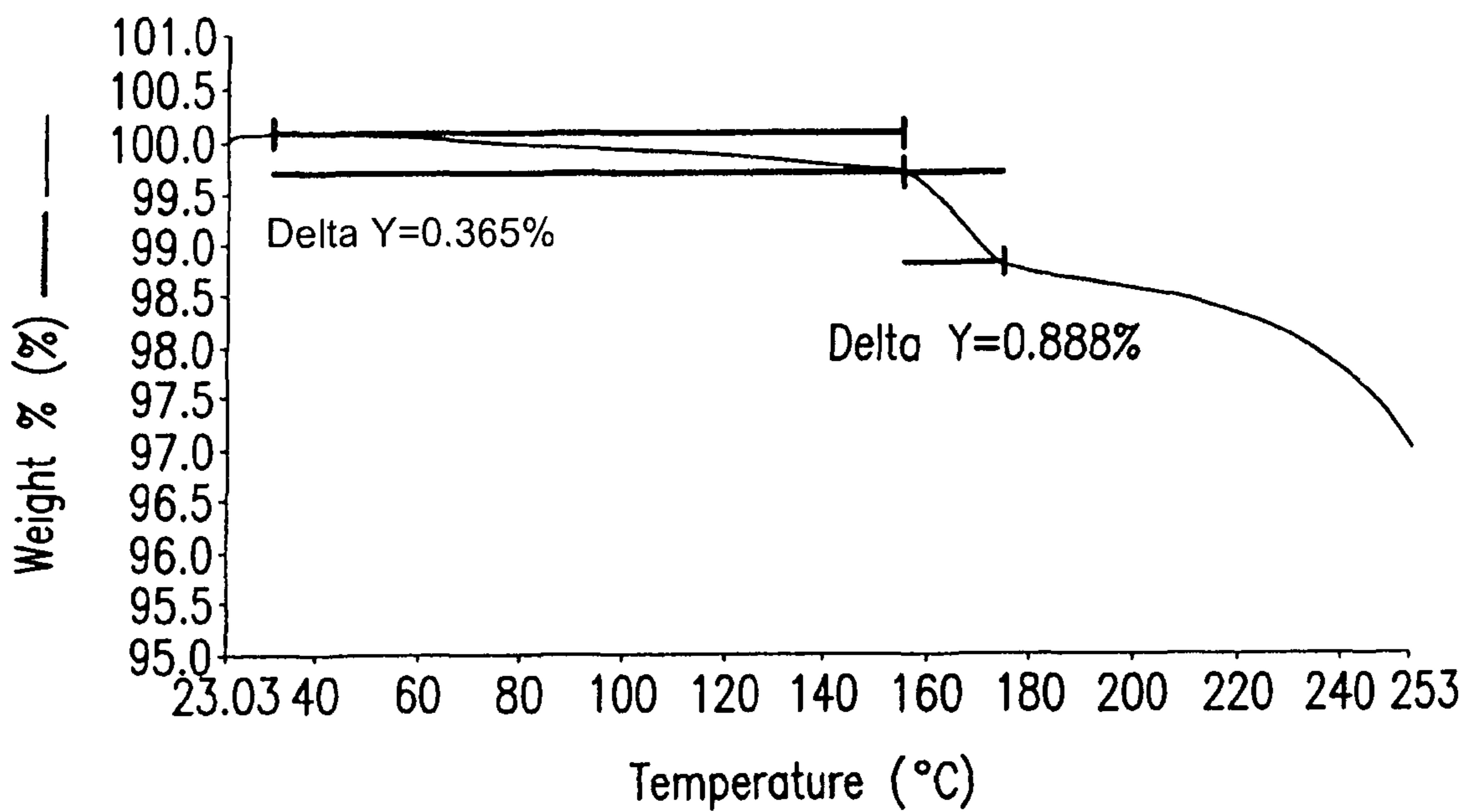


FIG.13

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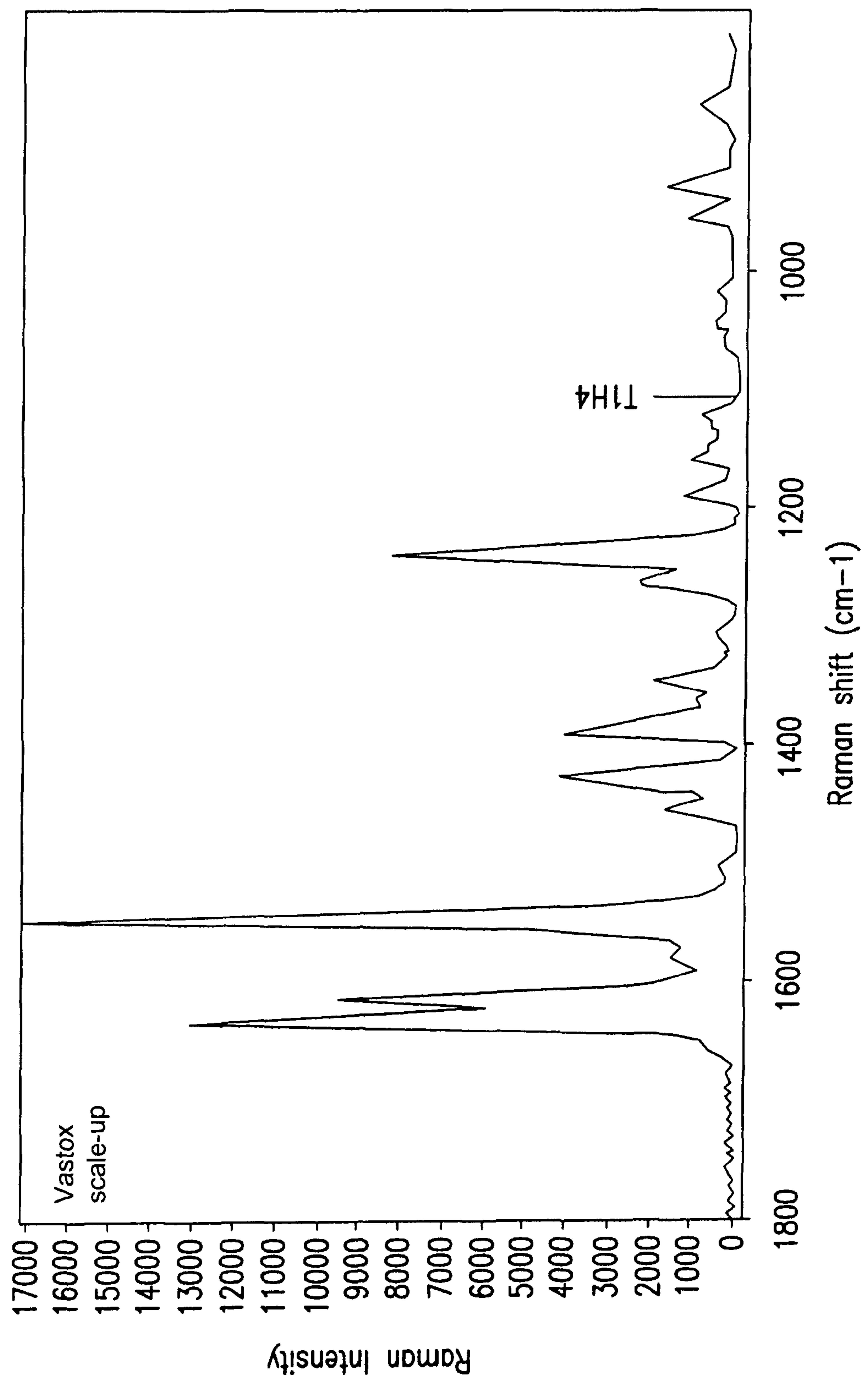


FIG. 14

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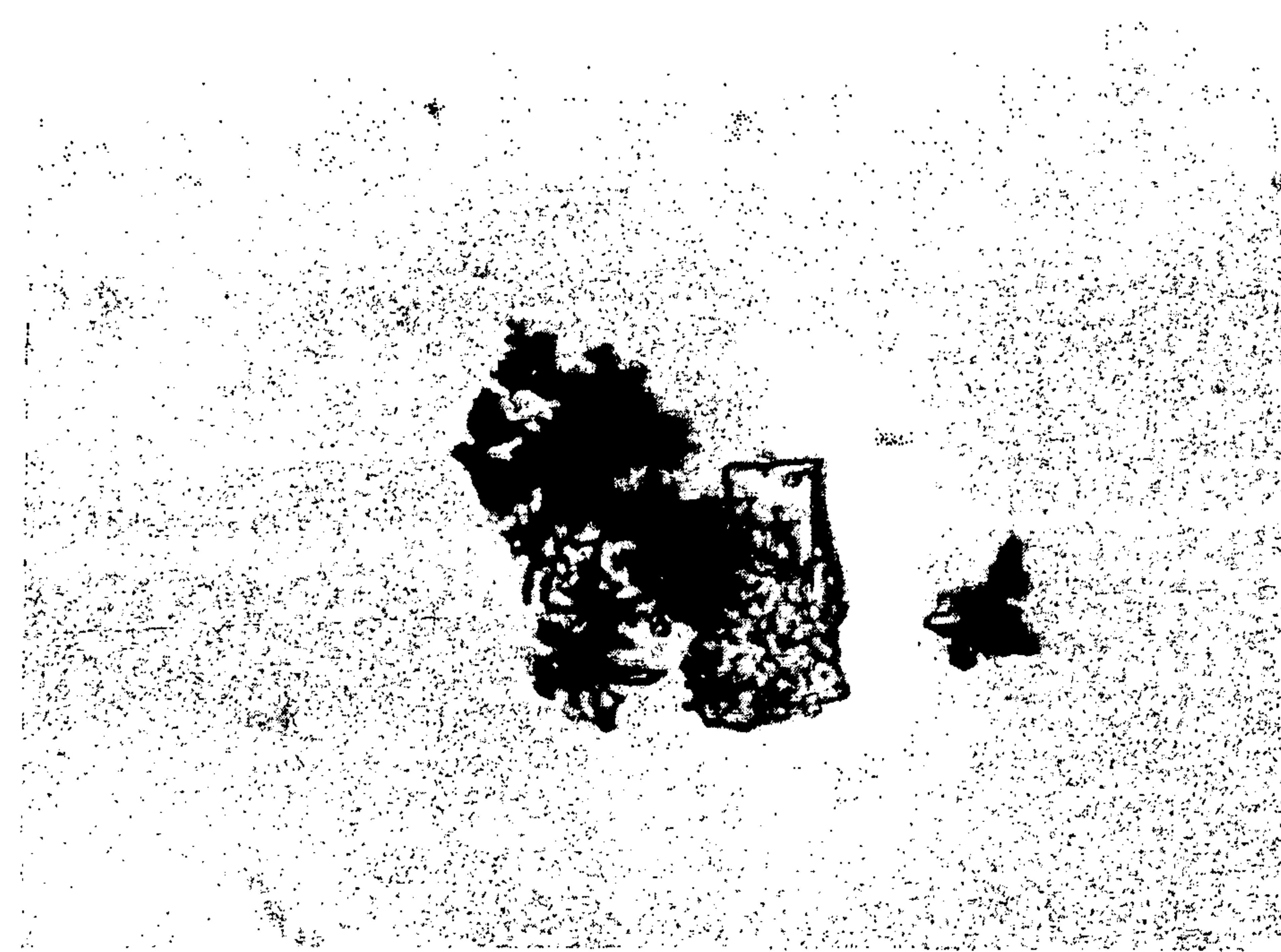


FIG.15

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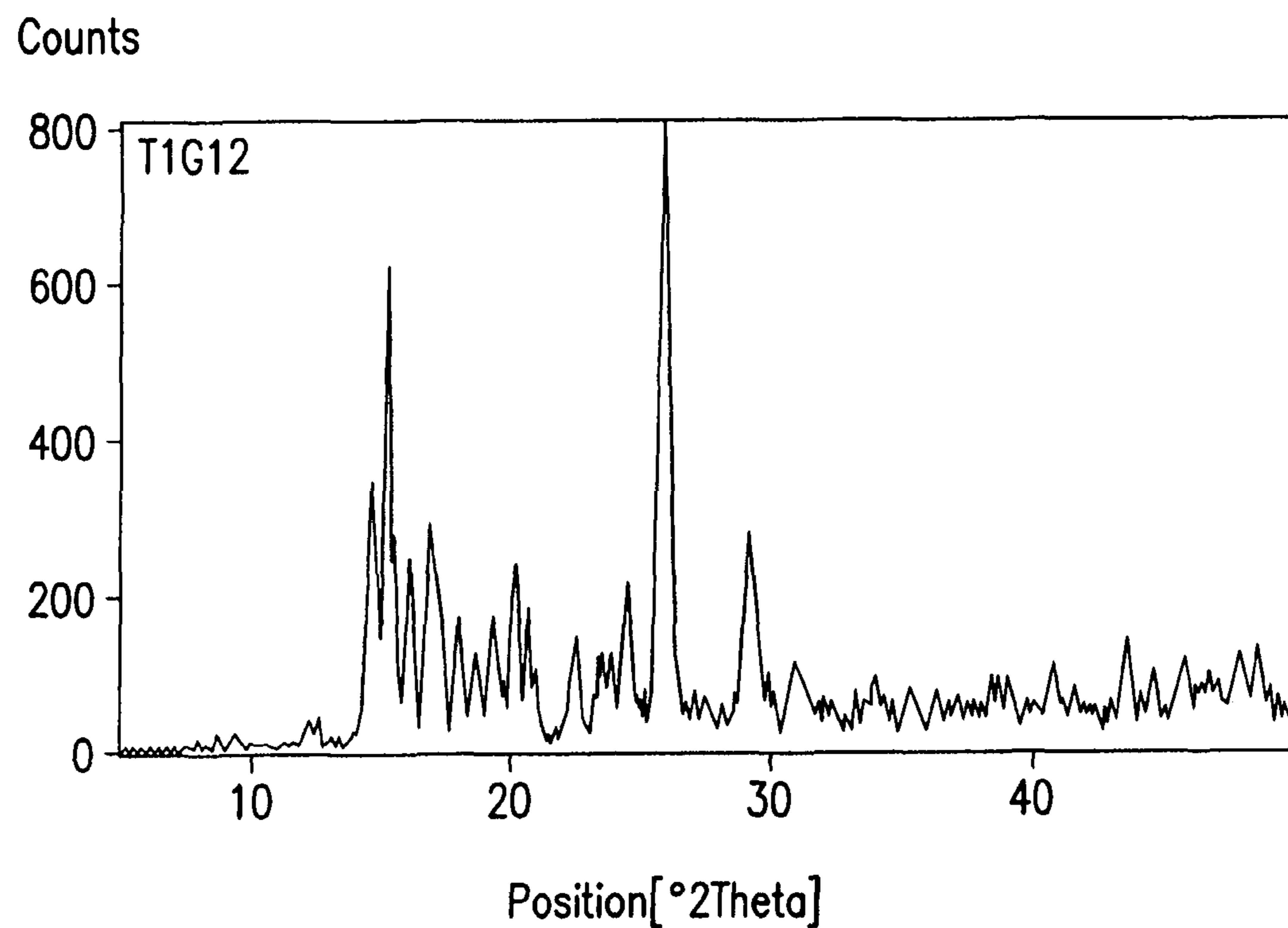


FIG. 16

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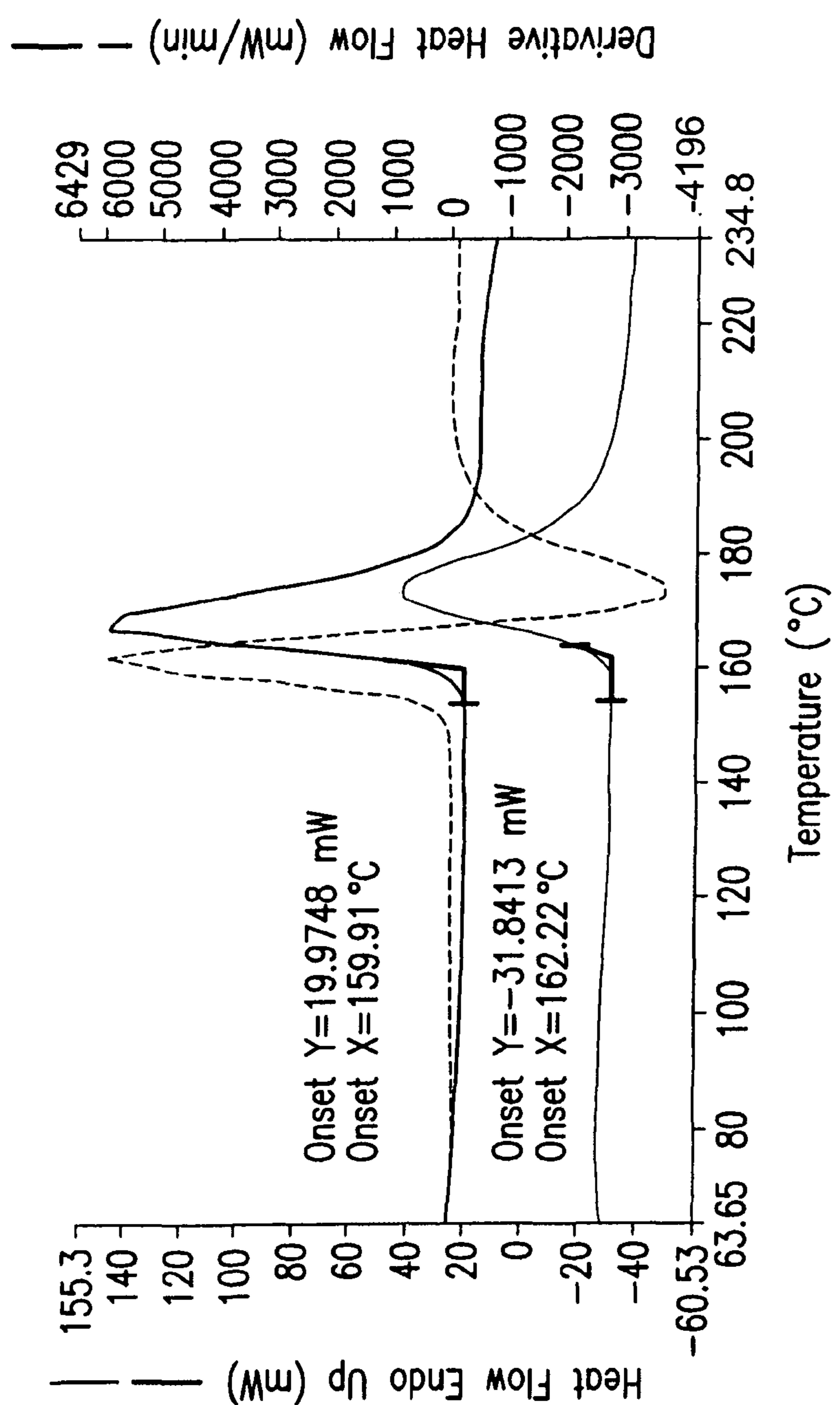


FIG. 17

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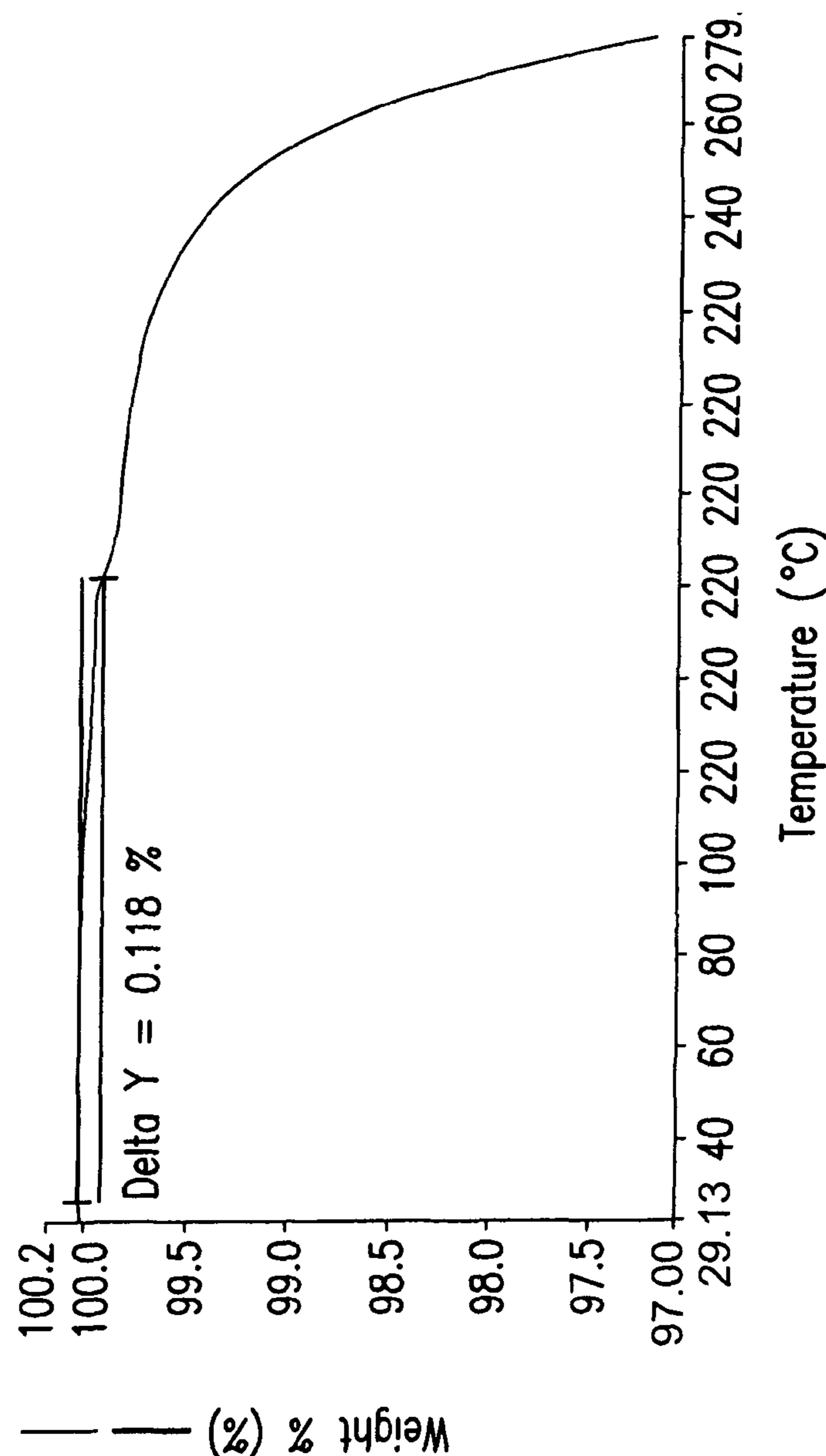


FIG. 18

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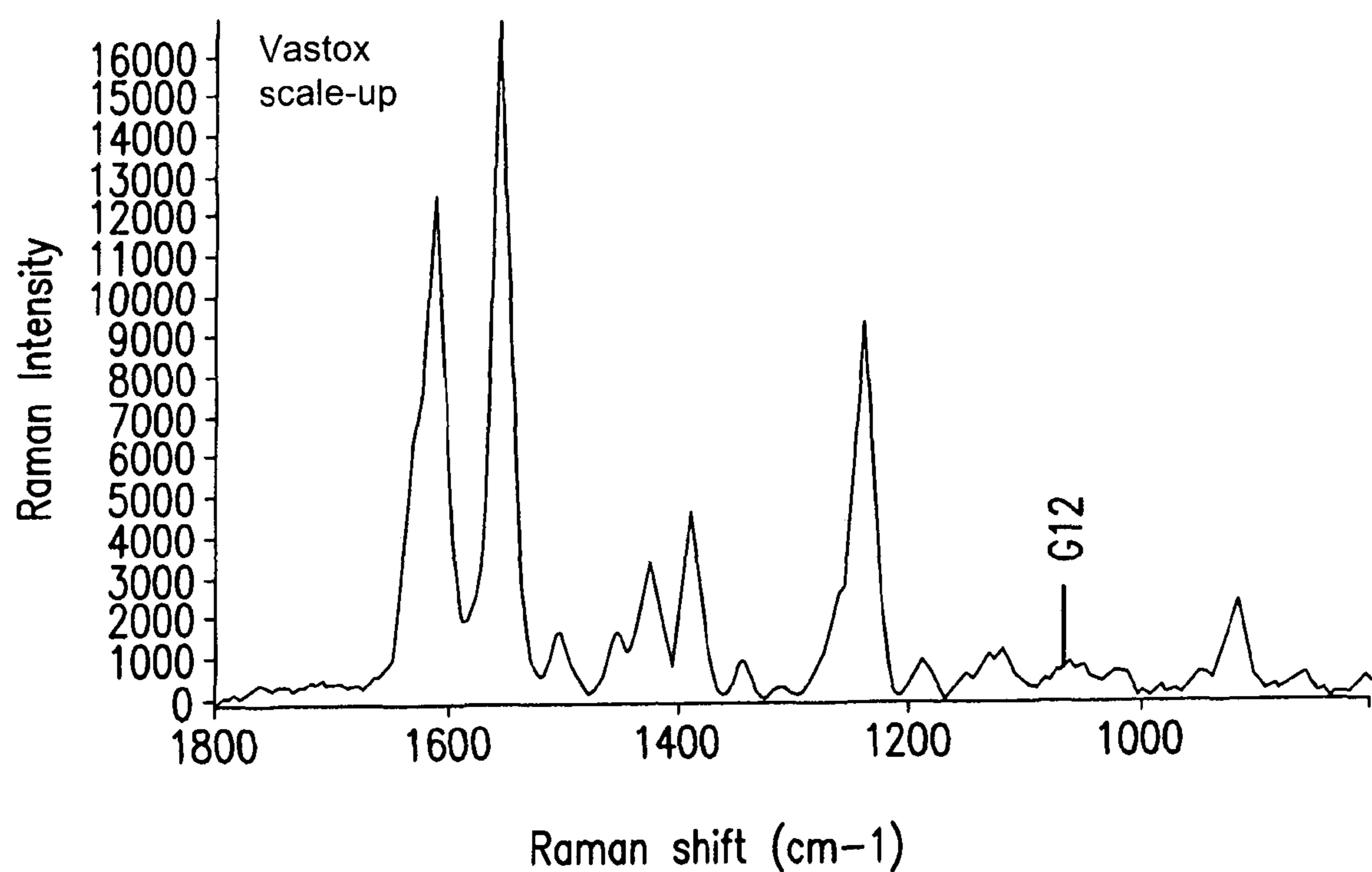


FIG. 19

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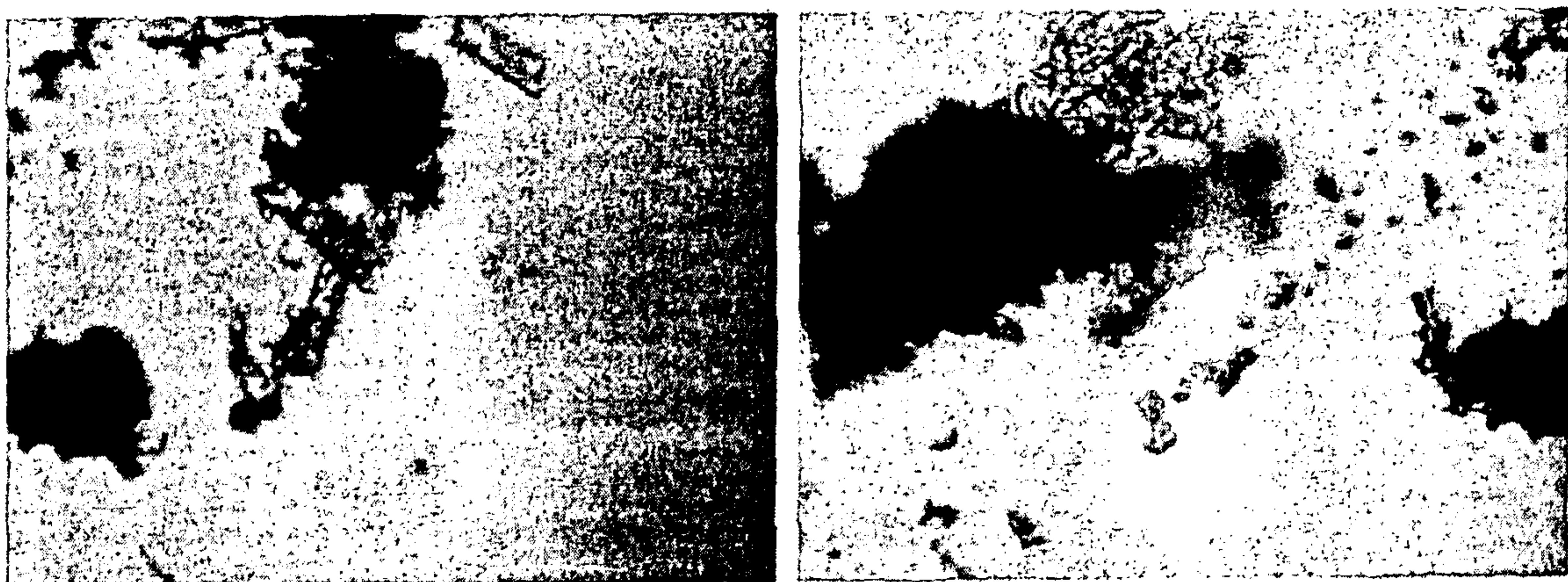
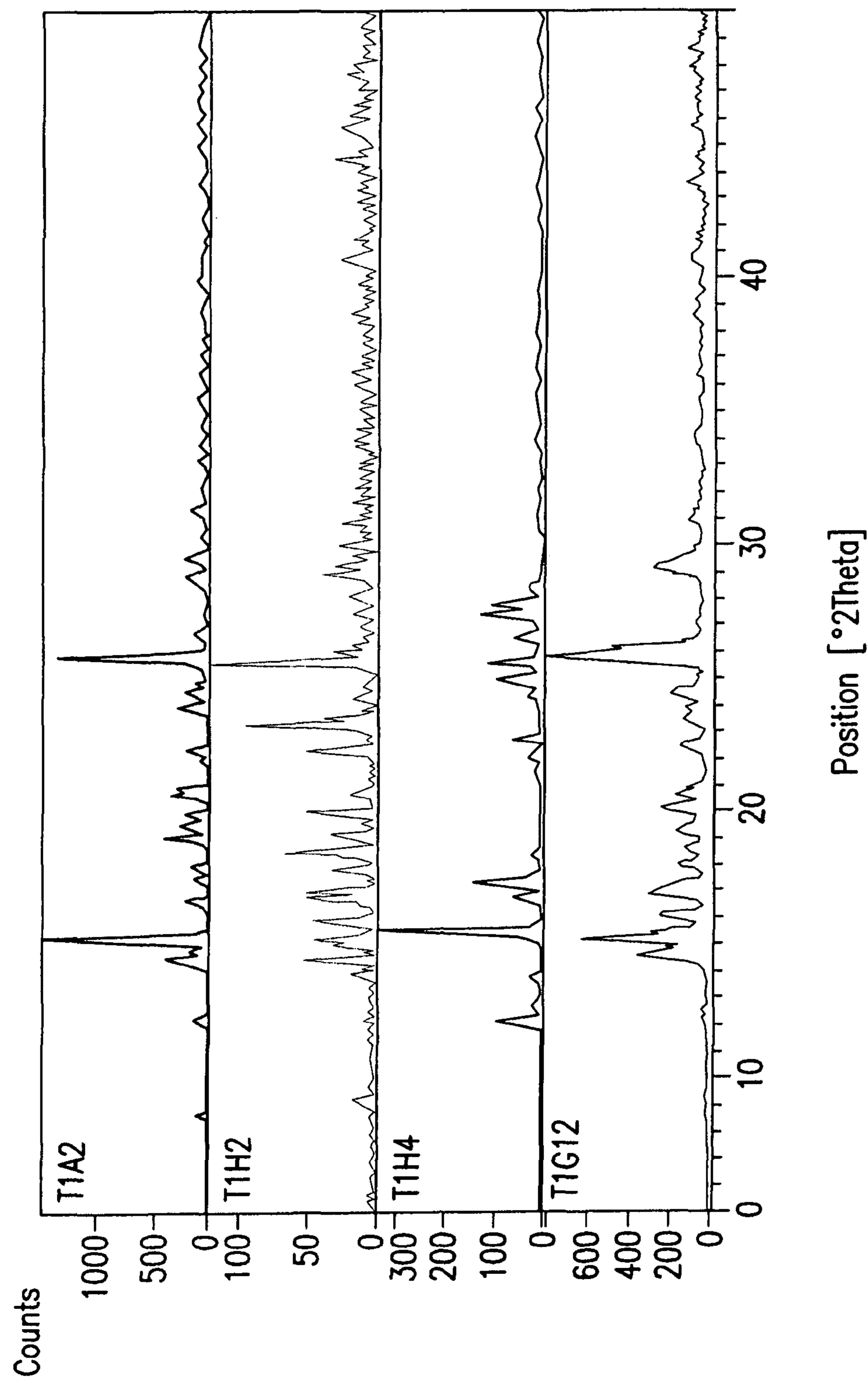


FIG.20

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Position [°2Theta]

FIG.21

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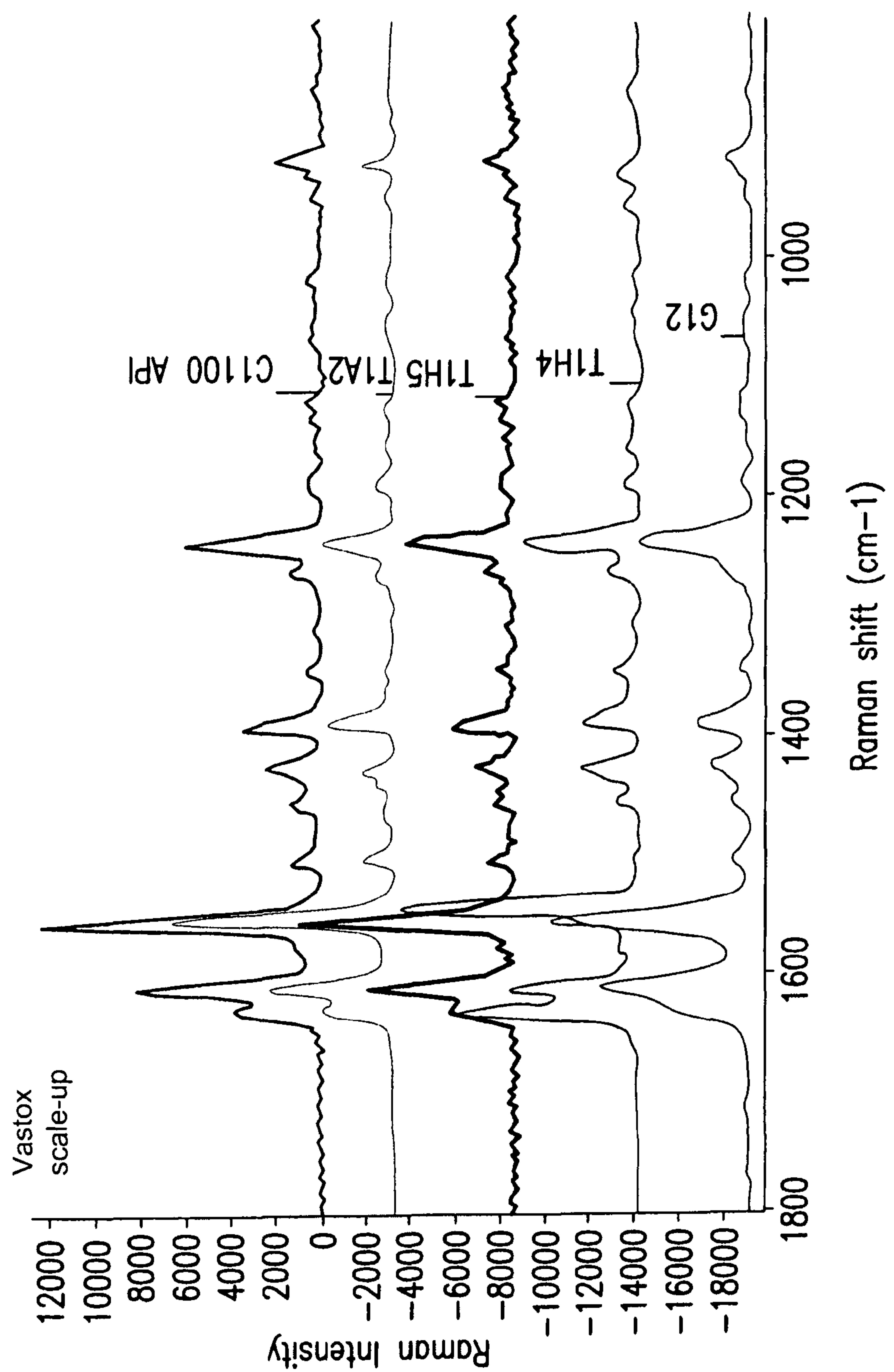


FIG.22

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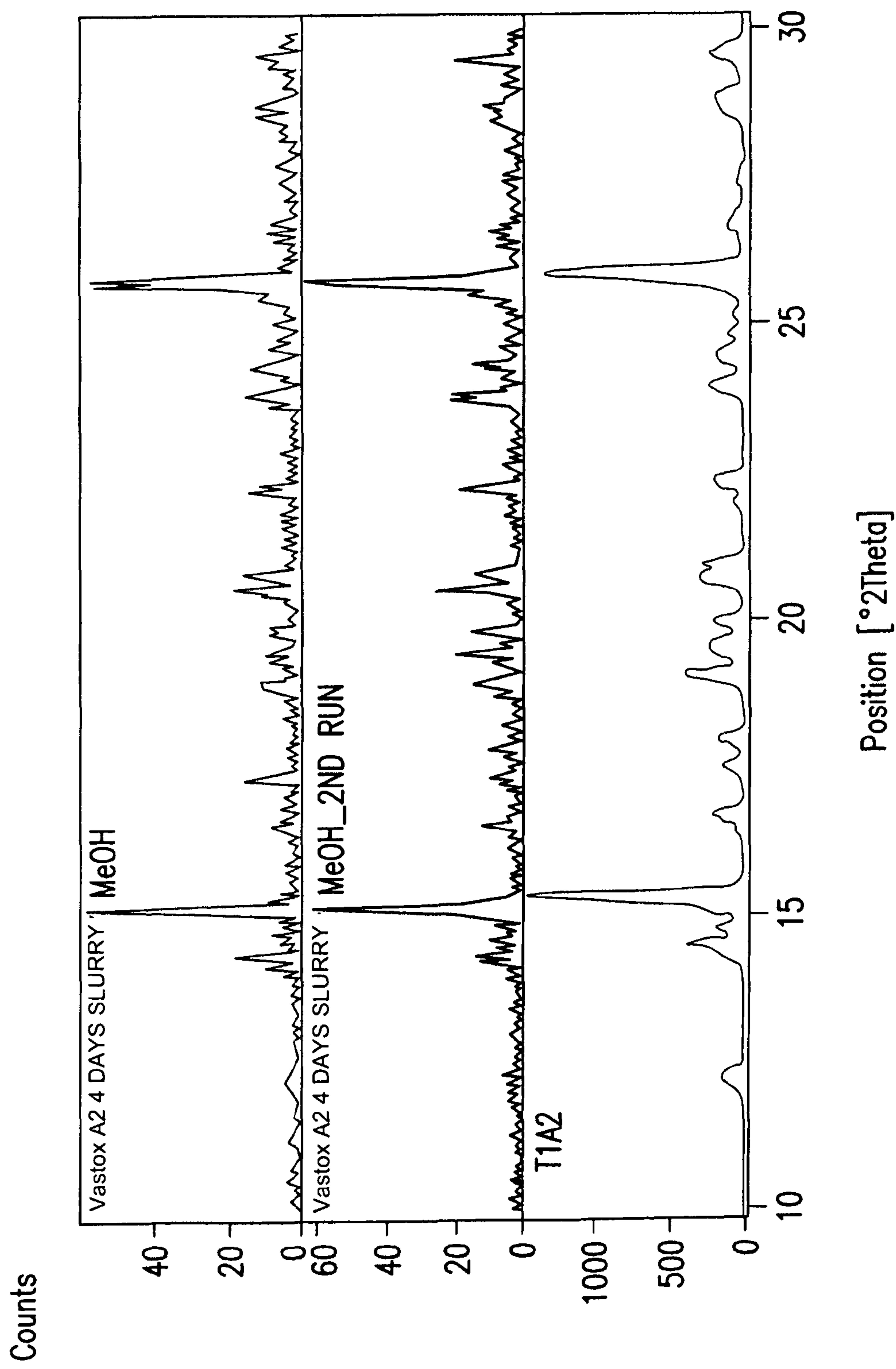
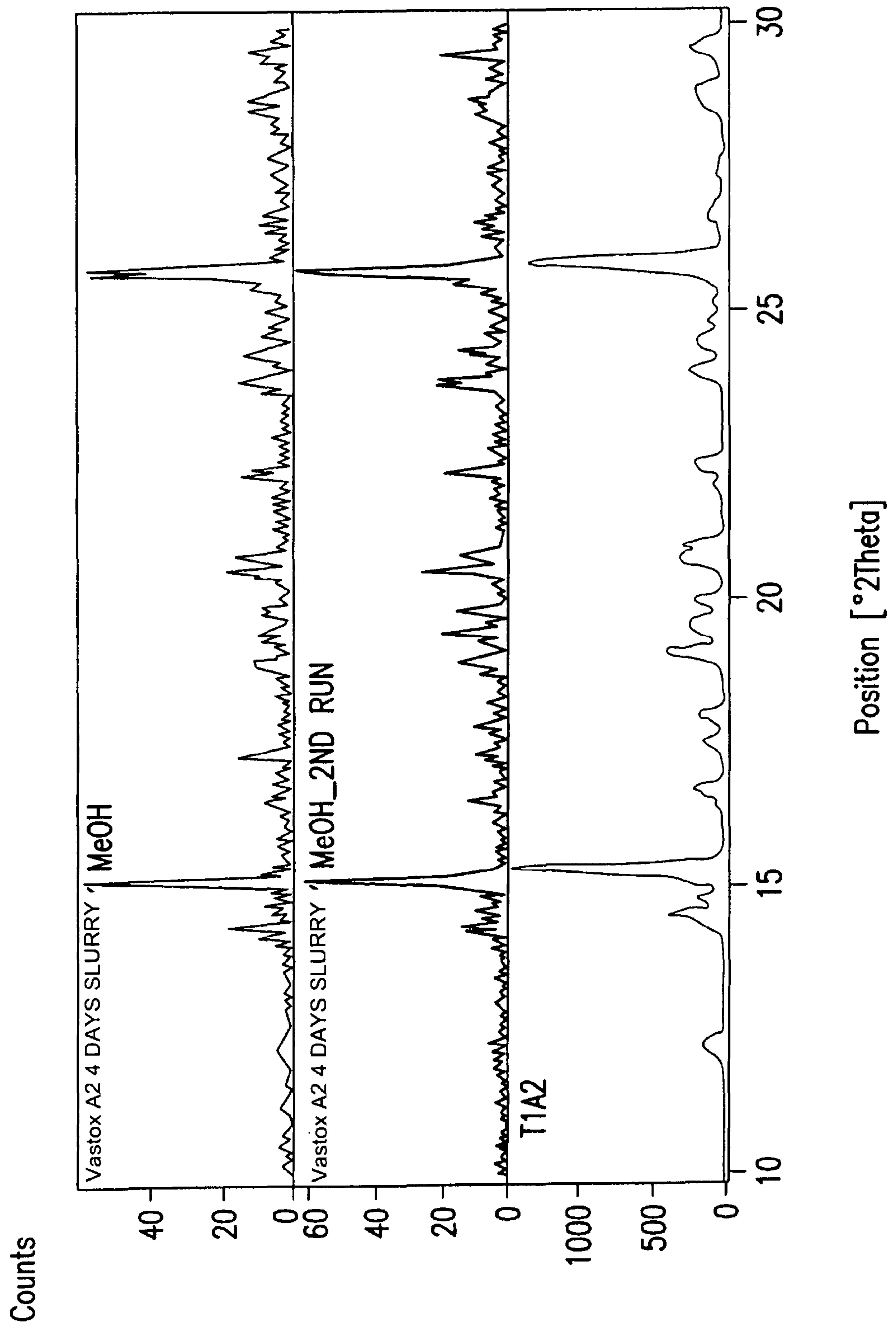


FIG.23

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Position [°2Theta]

FIG.24

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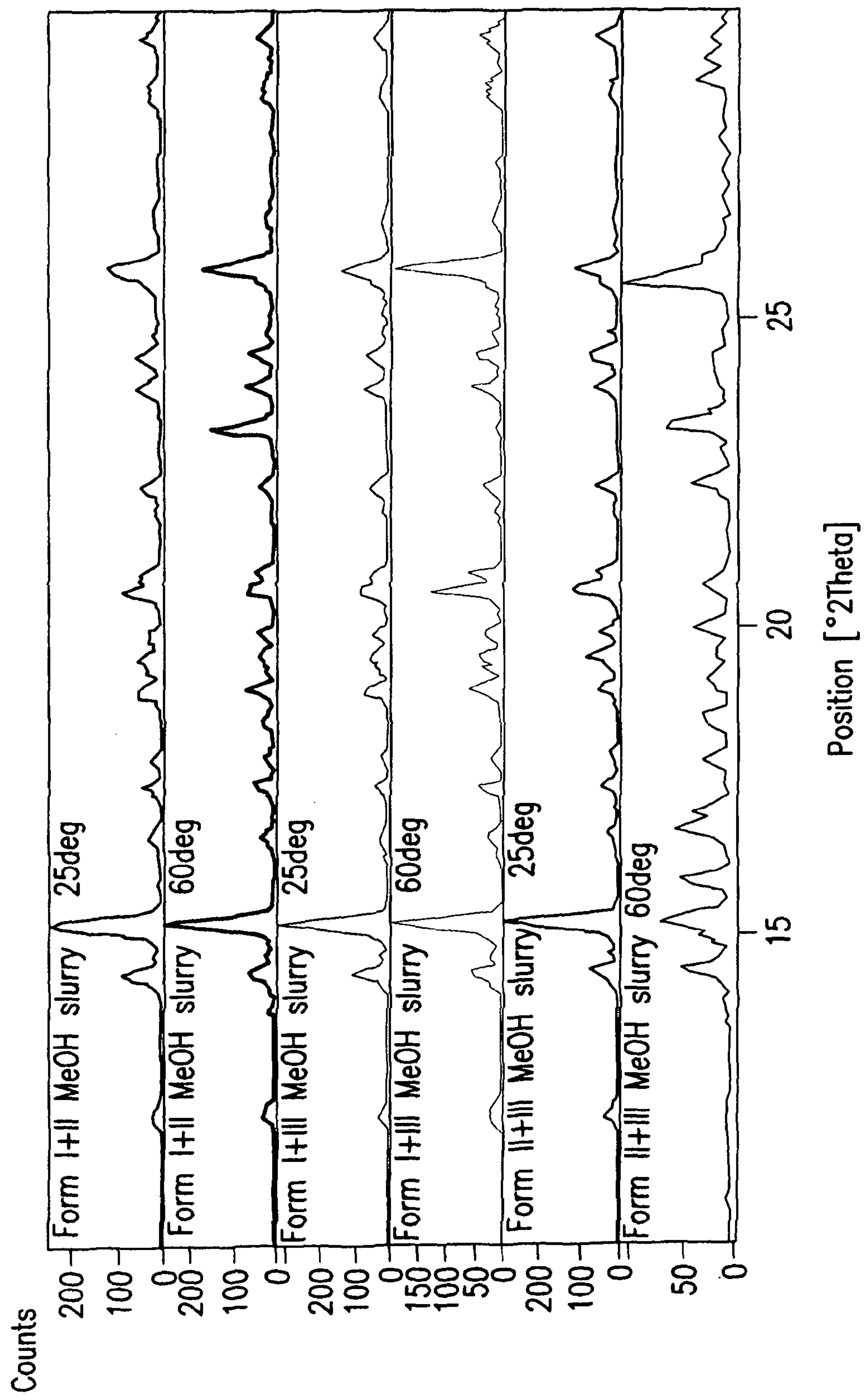


FIG. 25

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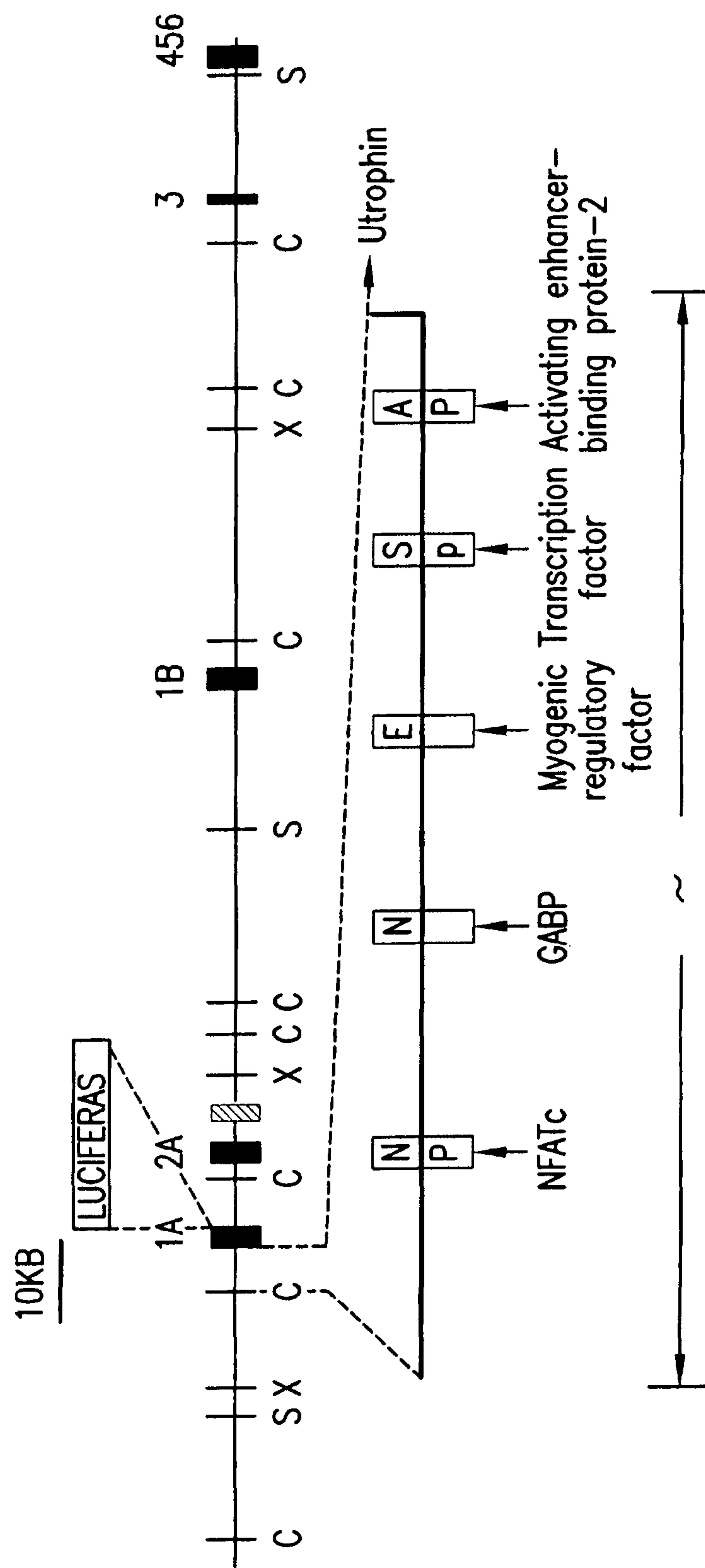
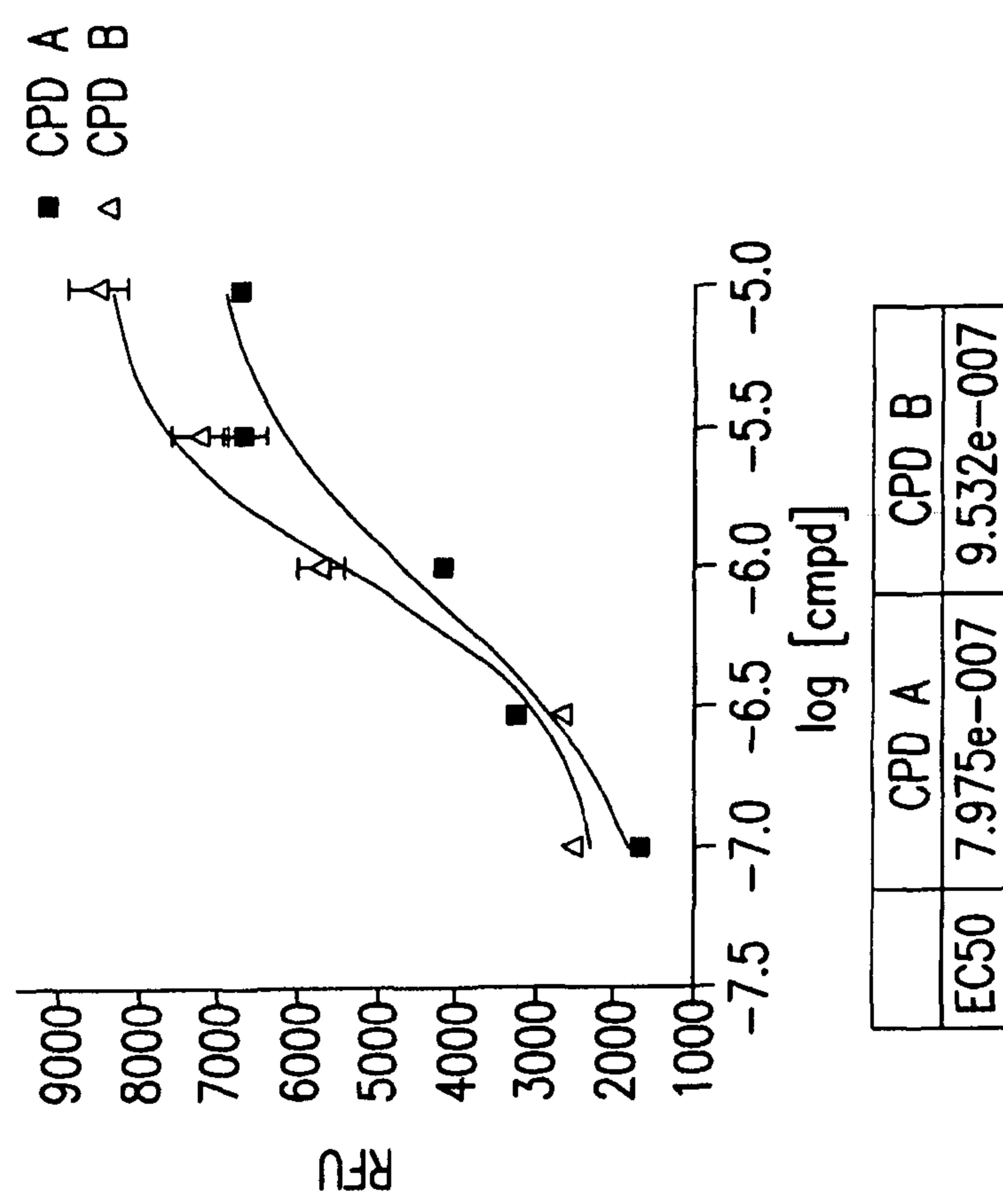


FIG. 26

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CPD A - 5-amino-2-(5,6-dimethylbenzo[d]oxazol-2-yl)phenol  
 CPD B - 2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine

FIG. 27

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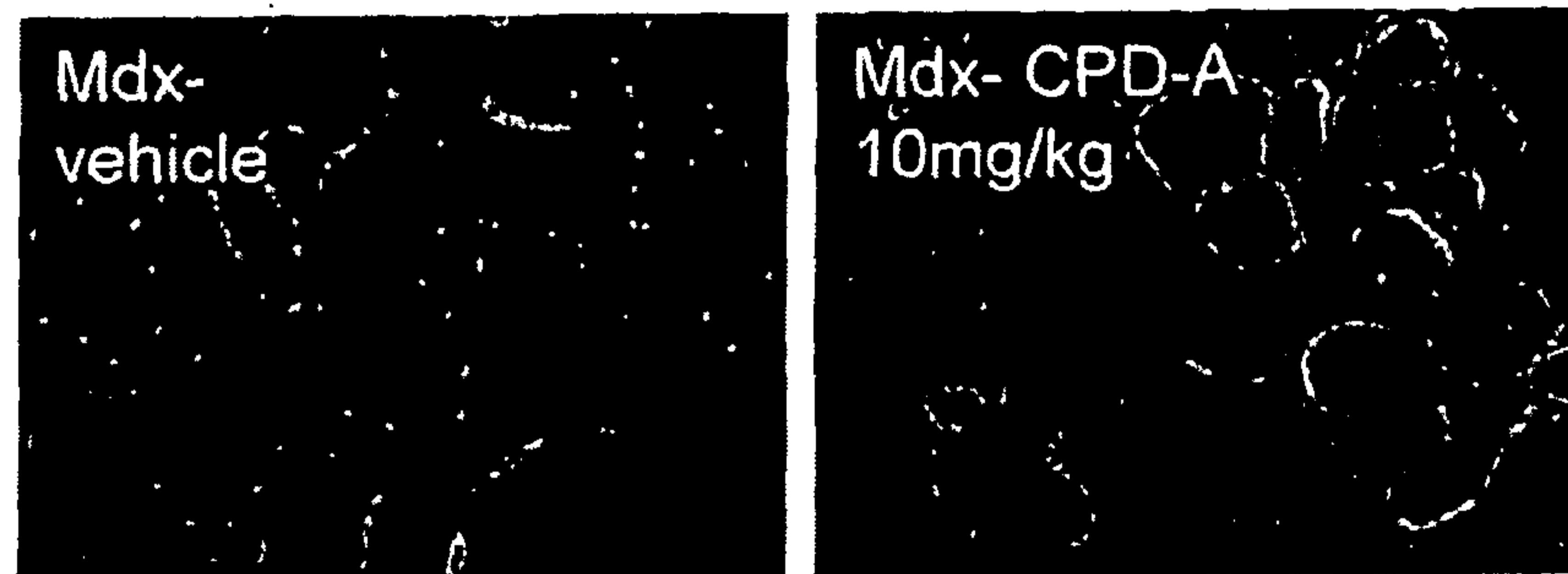


FIG. 28

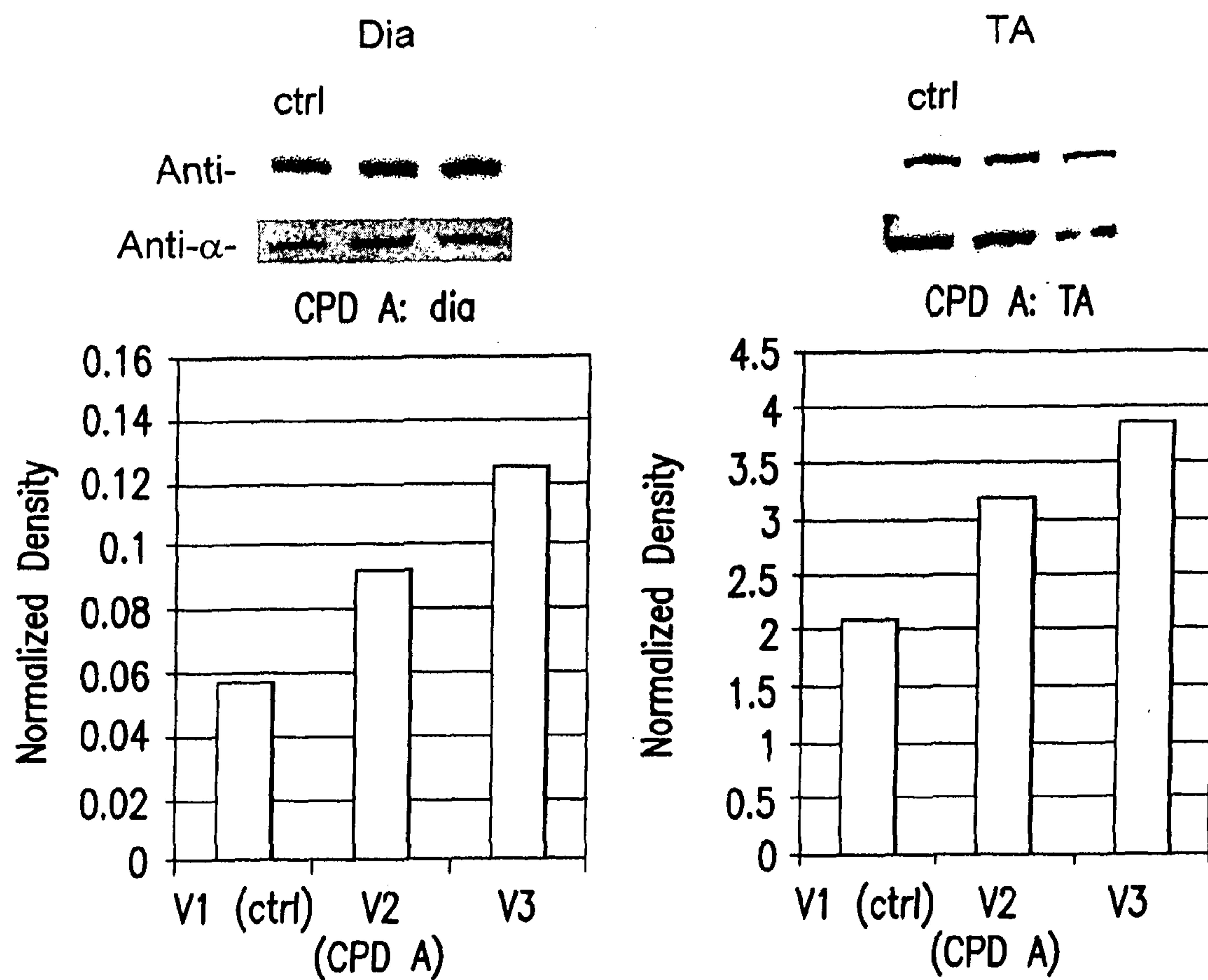


FIG. 29