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(54) **TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY**

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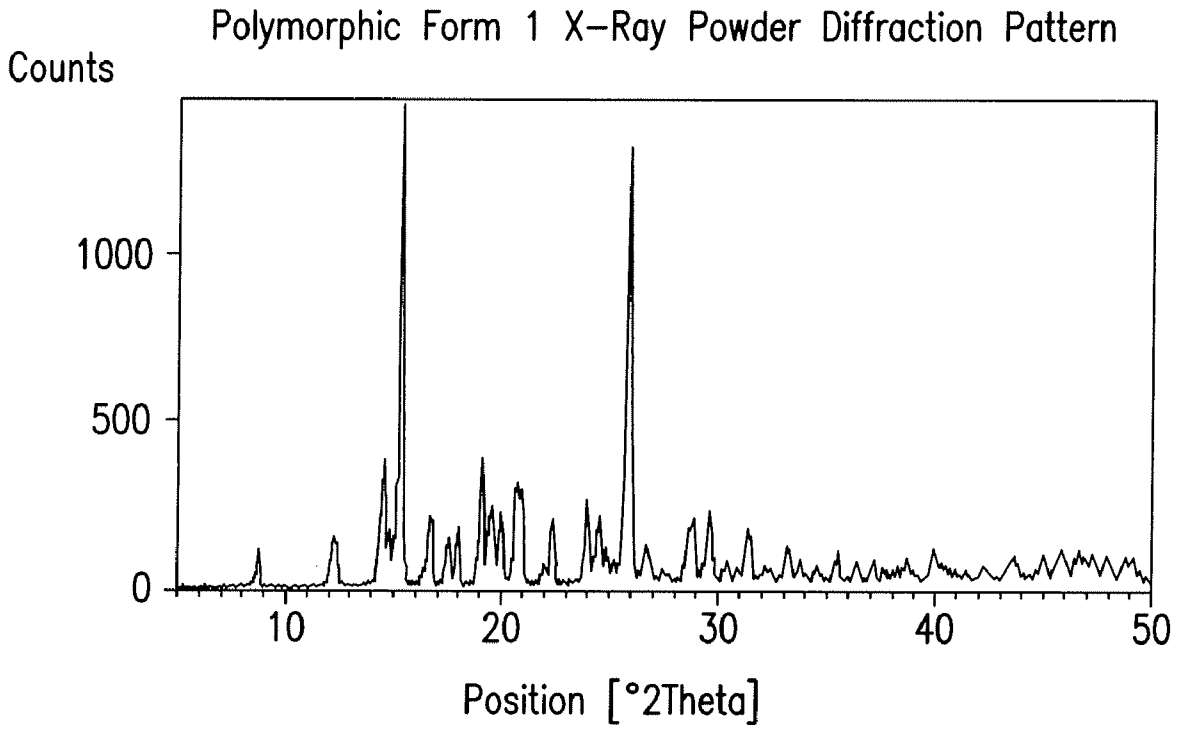
(57) **ABSTRACT**

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



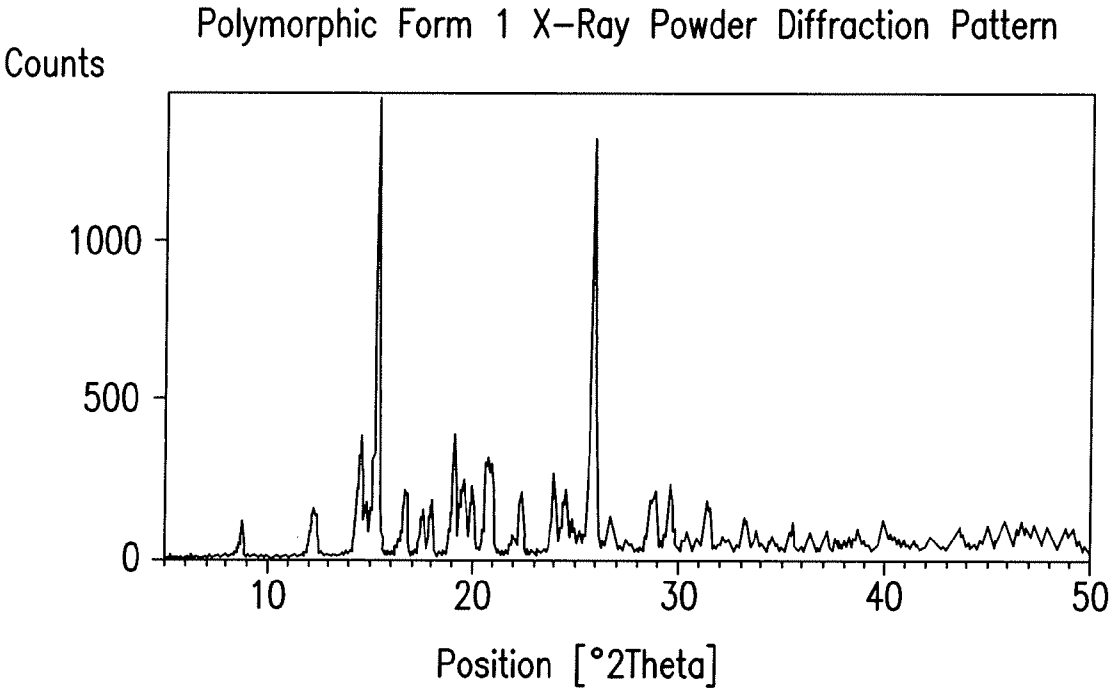

Polymorphic Form 1 X-Ray Powder Diffraction Pattern
Counts
1000
500
0
10
20
30
40
50
Position [°2Theta]

FIG. 1

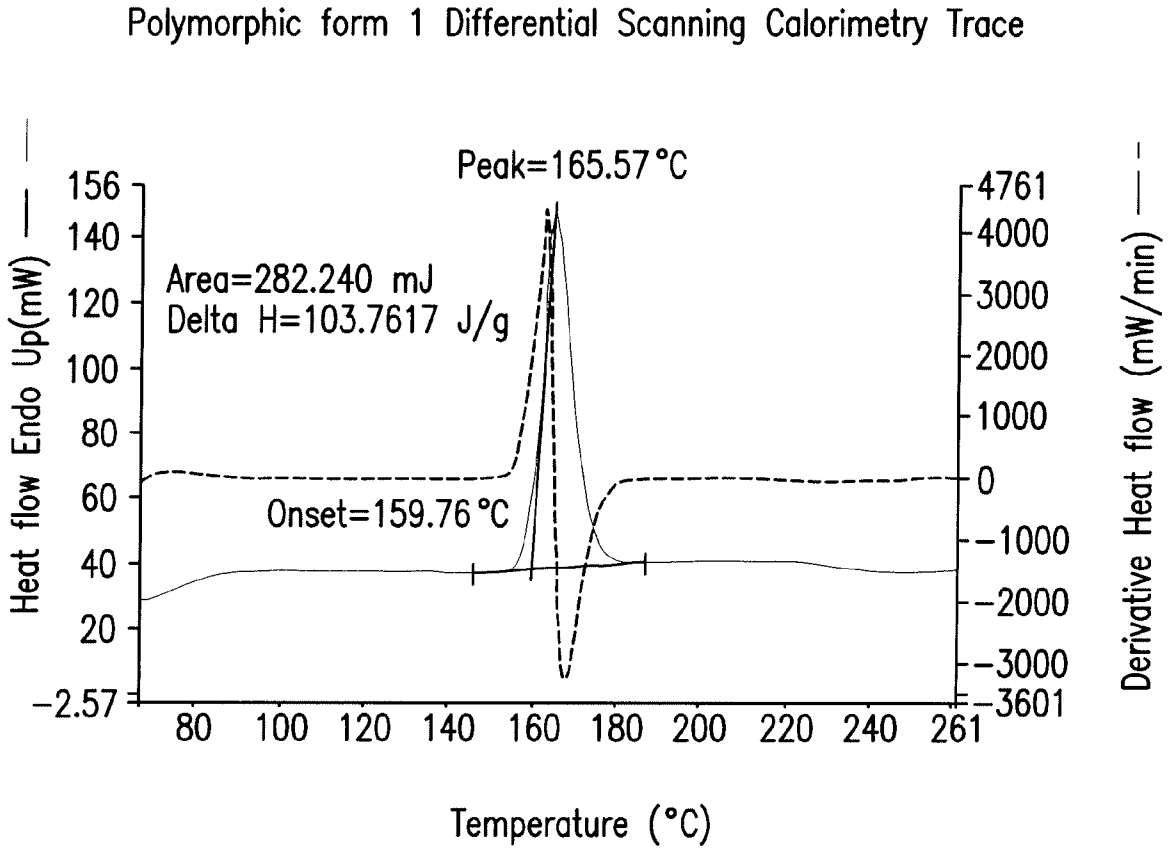

Polymorphic form 1 Differential Scanning Calorimetry Trace
Peak=165.57 °C
Area=282.240 mJ
Delta H=103.7617 J/g
Onset=159.76 °C
Heat flow Endo Up(mW)
Derivative Heat flow (mW/min)
Temperature (°C)
156
140
120
100
80
60
40
20
-2.57
4761
4000
3000
2000
1000
0
-1000
-2000
-3000
-3601
80
100
120
140
160
180
200
220
240
261

FIG.2

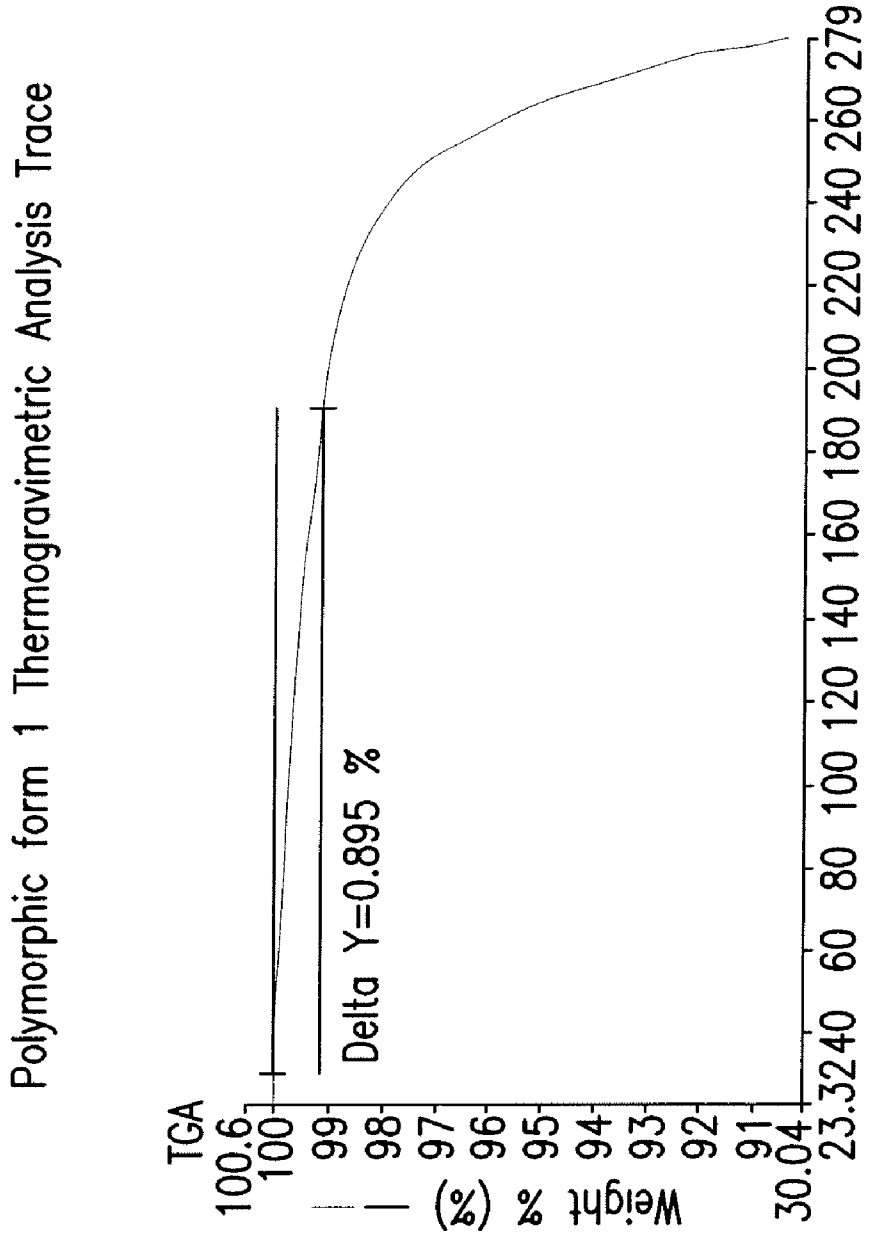

Polymorphic form 1 Thermogravimetric Analysis Trace
TGA
100.6
100
99
98
97
96
95
94
93
92
91
30.04
Weight % (%)
Delta Y=0.895 %
23.3240 60 80 100 120 140 160 180 200 220 240 260 279
Temperature (°C)

FIG.3

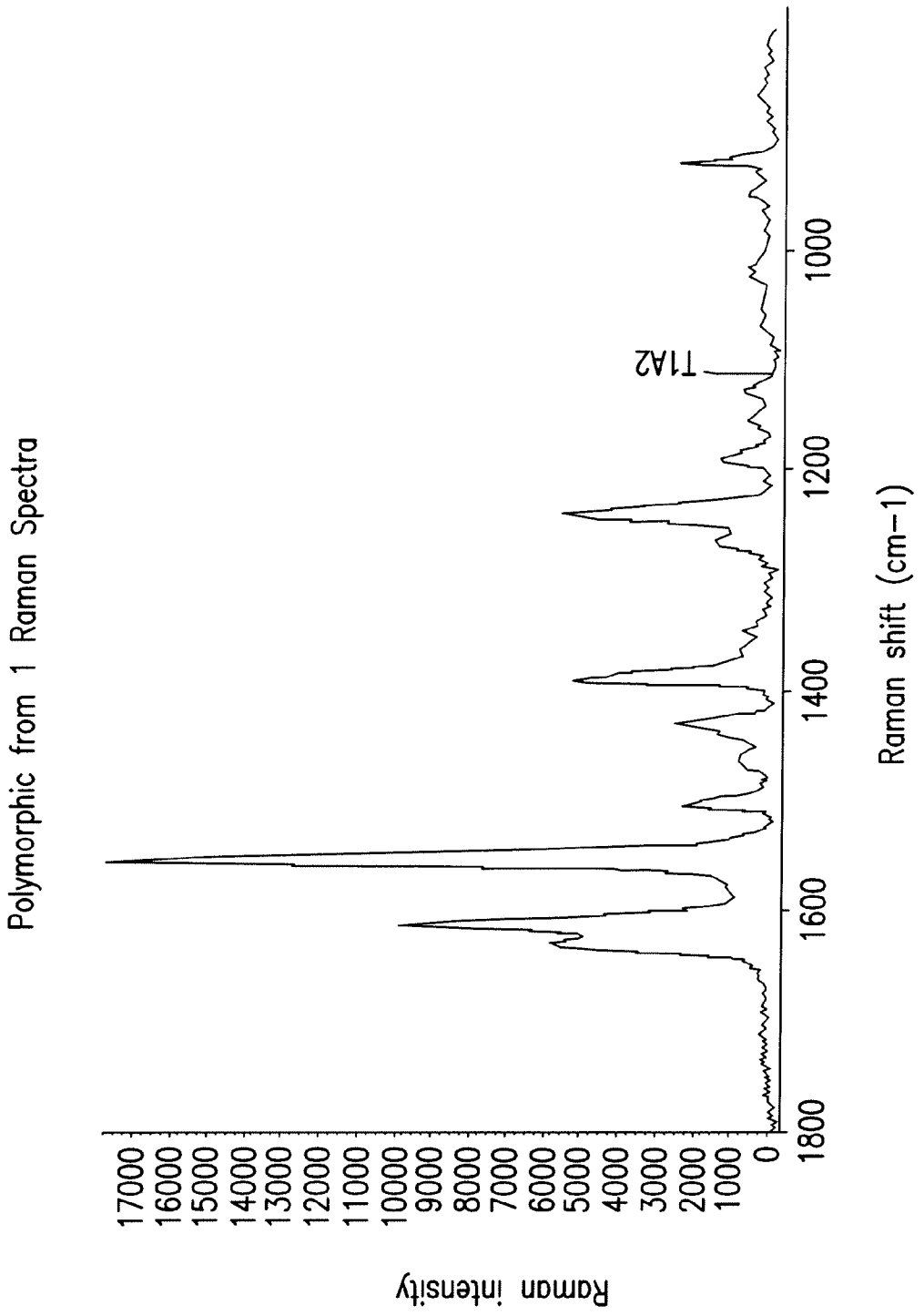
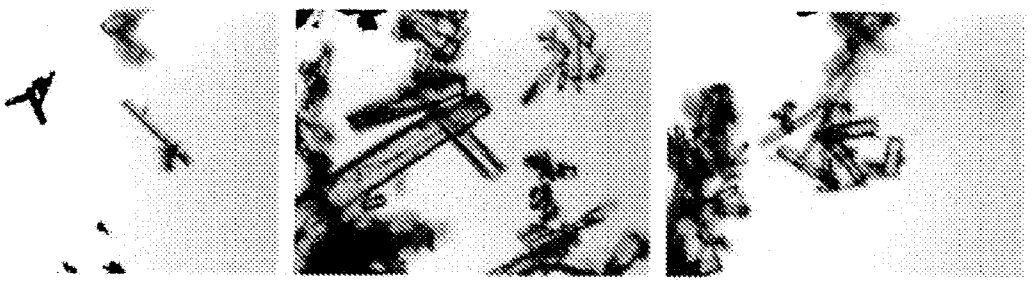

Polymorphic from 1 Raman Spectra
Raman intensity
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1800
1600
1400
1200
1000
Raman shift (cm−1)
T1A2

FIG.4

Polymorphic form 1 Optical Microscope Images



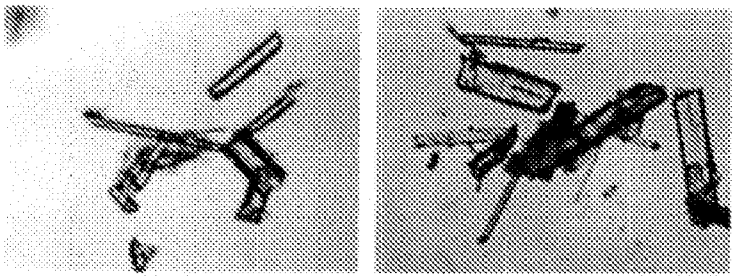


FIG. 5

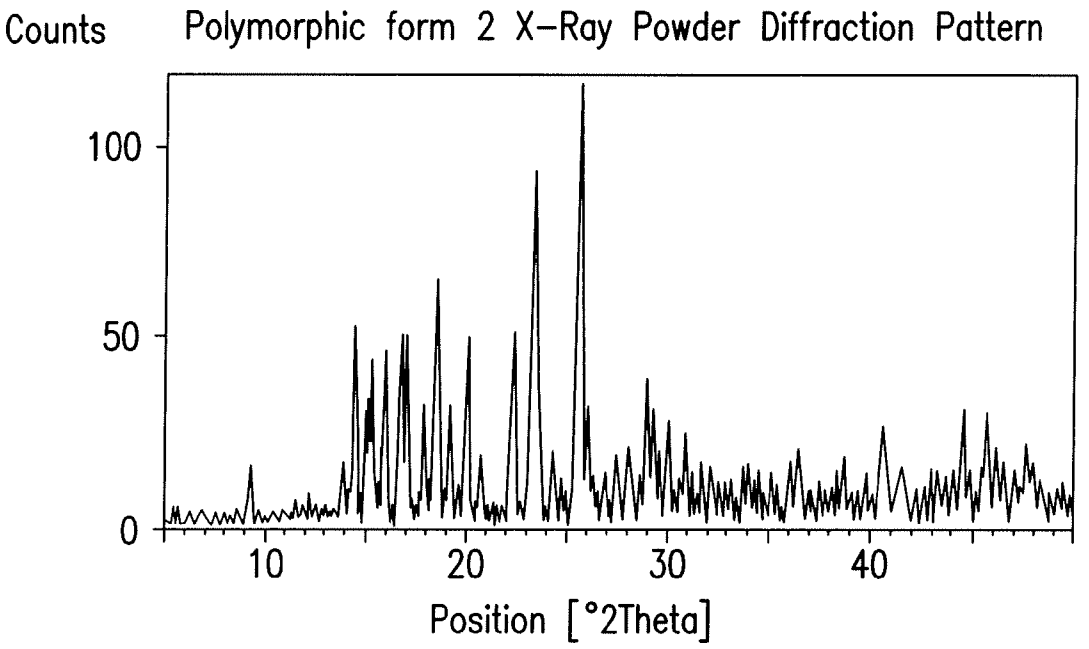

Counts
Polymorphic form 2 X-Ray Powder Diffraction Pattern
100
50
0
10
20
30
40
Position [°2Theta]

FIG.6

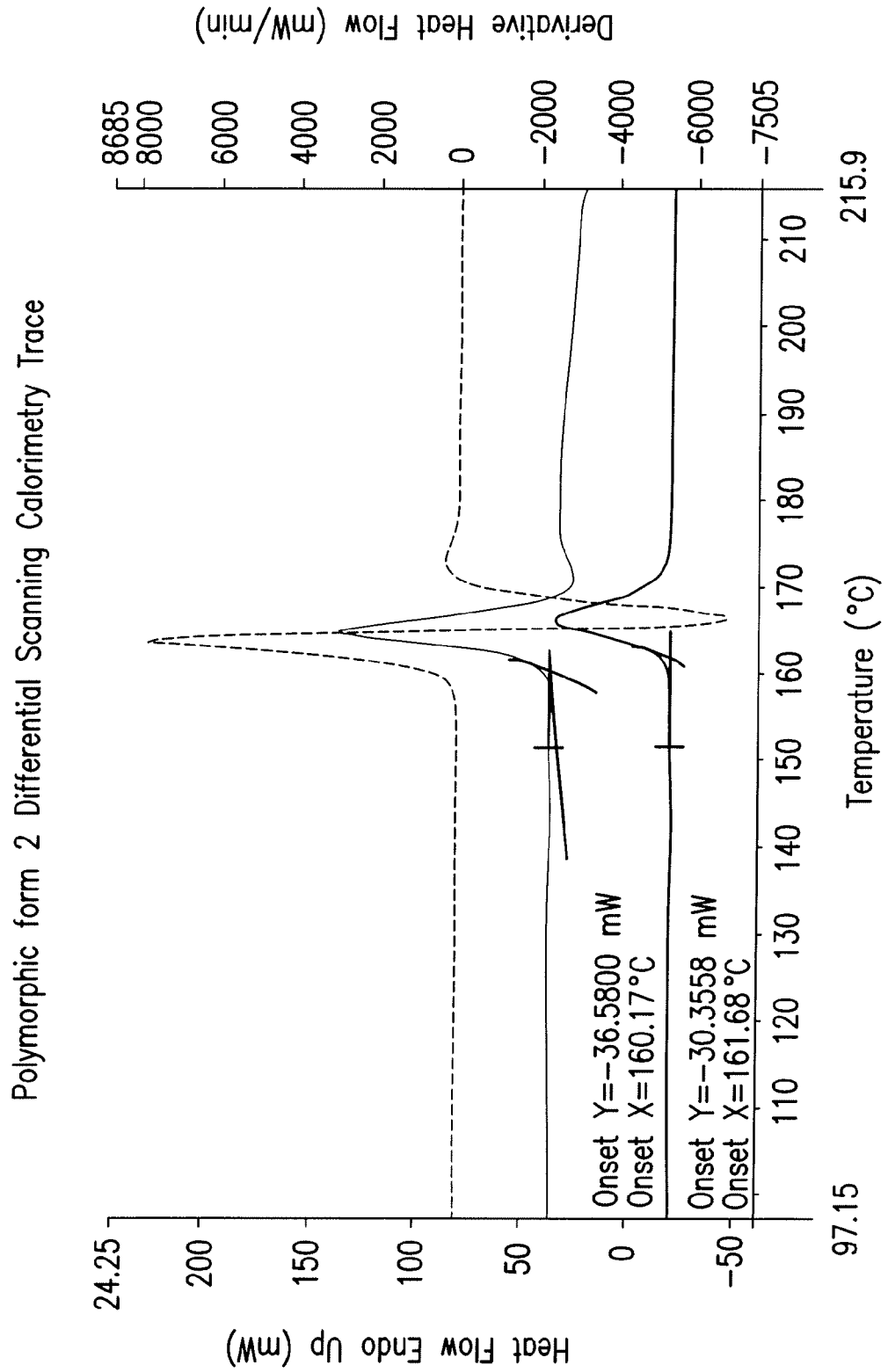

Polymorphic form 2 Differential Scanning Calorimetry Trace
Heat Flow Endo Up (mW)
Derivative Heat Flow (mW/min)
Temperature (°C)
24.25
200
150
100
50
0
−50
97.15
8685
8000
6000
4000
2000
0
−2000
−4000
−6000
−7505
110
120
130
140
150
160
170
180
190
200
210
215.9
Onset Y=−36.5800 mW
Onset X=160.17°C
Onset Y=−30.3558 mW
Onset X=161.68°C

FIG. 7

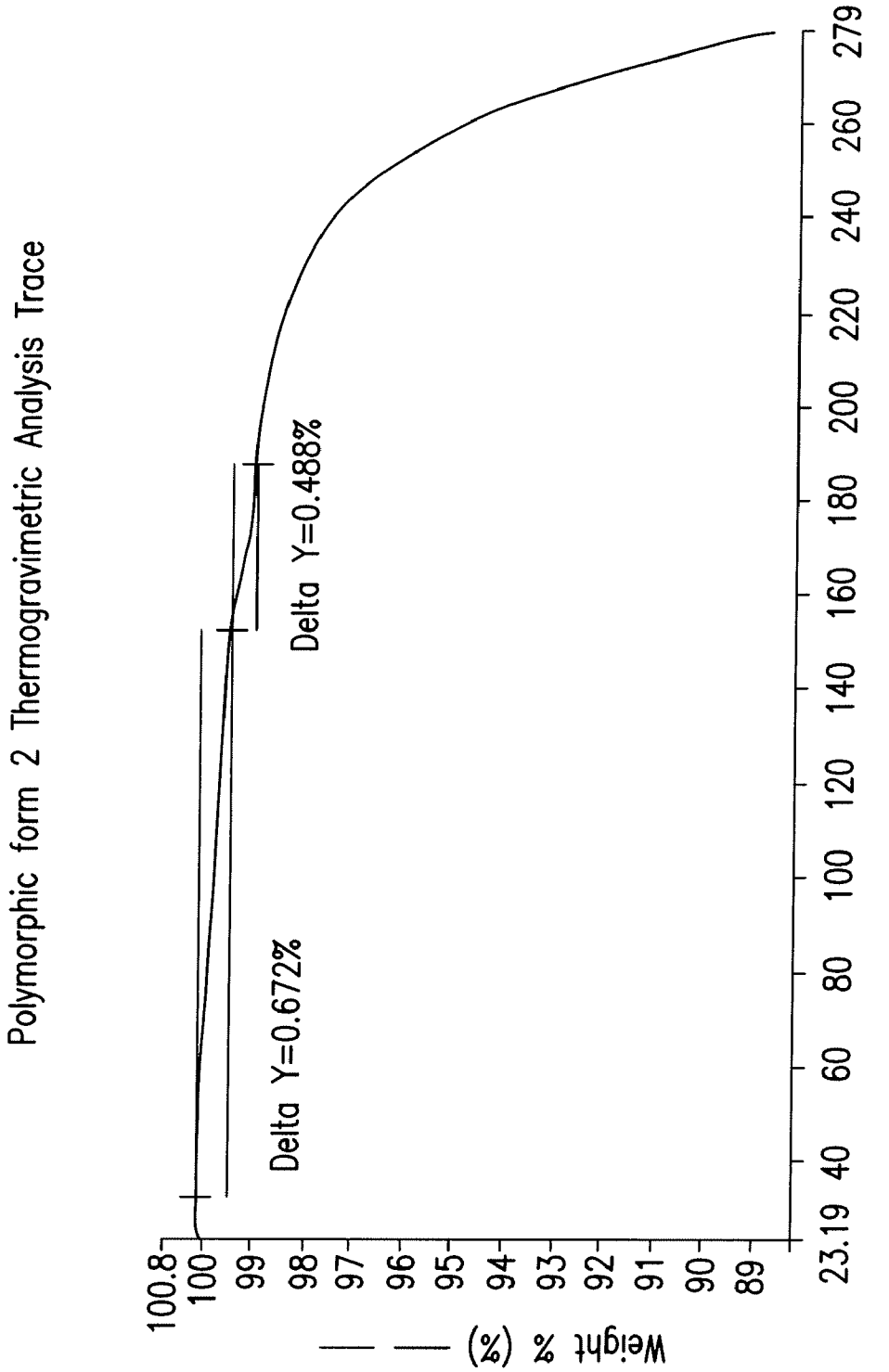

Polymorphic form 2 Thermogravimetric Analysis Trace
Delta Y=0.672%
Delta Y=0.488%
Weight % (%)
Temperature (°C)
100.8
100
99
98
97
96
95
94
93
92
91
90
89
23.19
40
60
80
100
120
140
160
180
200
220
240
260
279

FIG.8

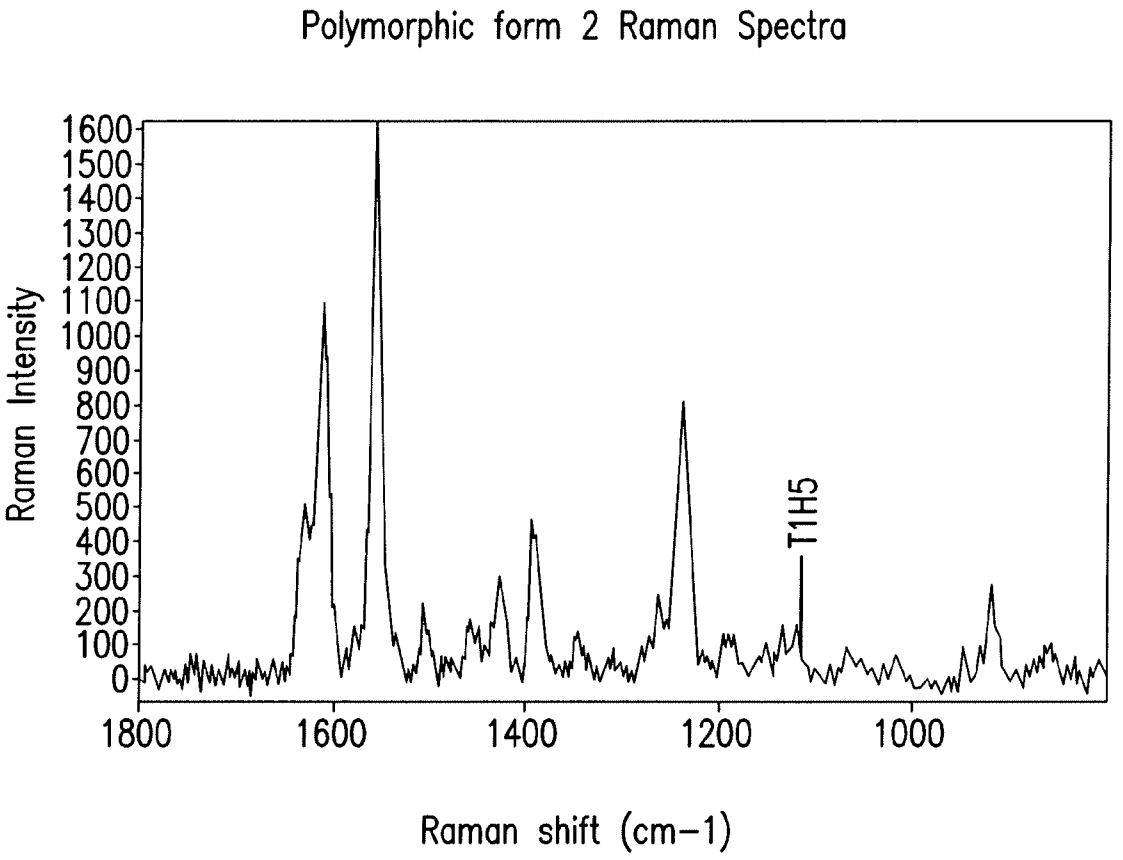

Polymorphic form 2 Raman Spectra
Raman Intensity
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
T1H5
1800
1600
1400
1200
1000
Raman shift (cm−1)

FIG.9

Polymorphic form 2 Optical Microscope Images

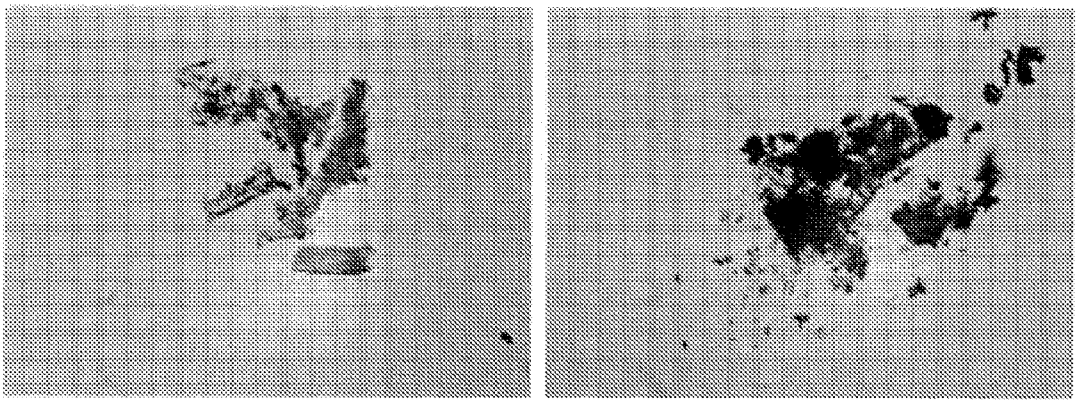


FIG. 10

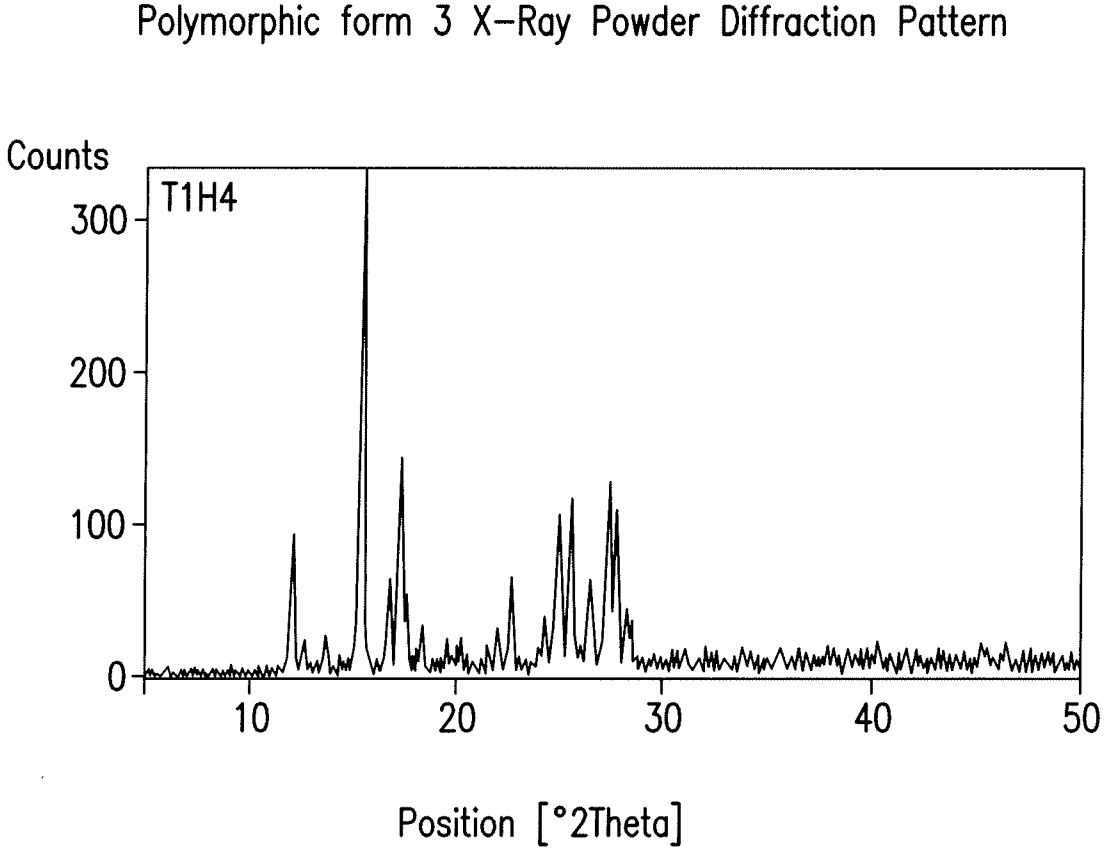

Polymorphic form 3 X-Ray Powder Diffraction Pattern
Counts
T1H4
300
200
100
0
10
20
30
40
50
Position [°2Theta]

FIG. 11

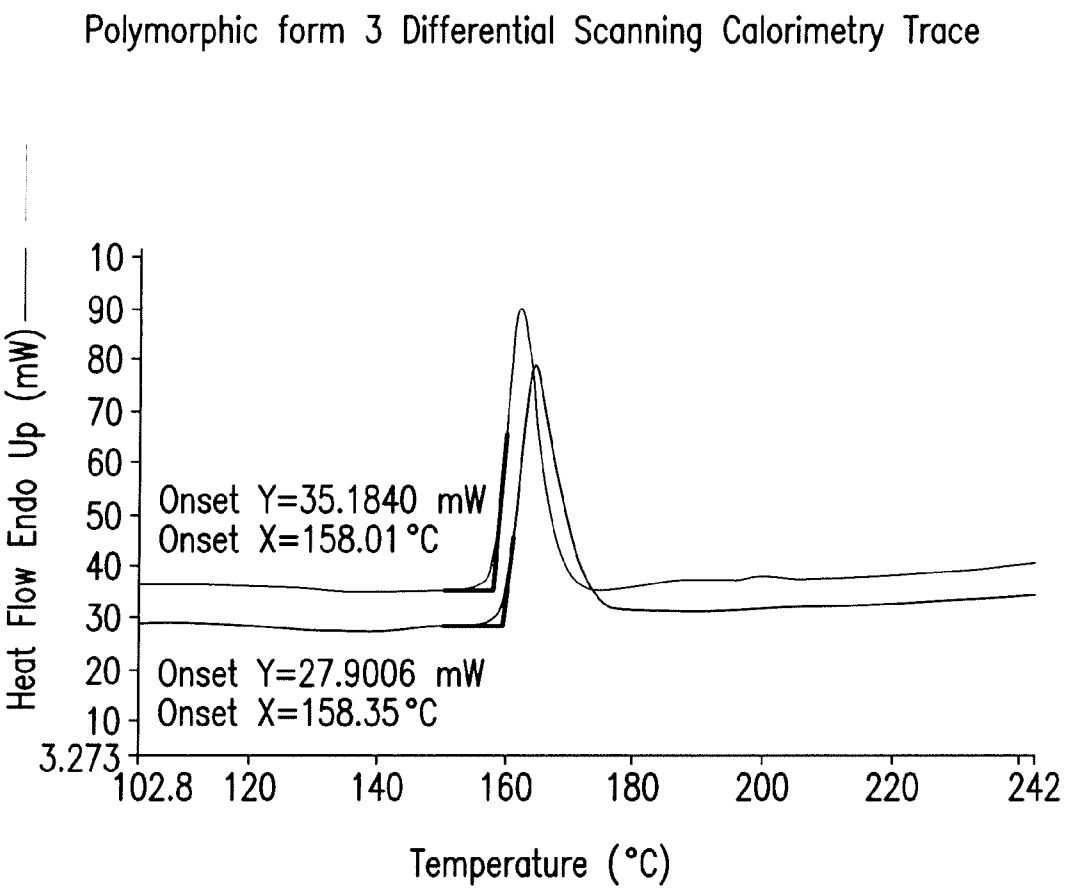

Polymorphic form 3 Differential Scanning Calorimetry Trace
Heat Flow Endo Up (mW)
10
90
80
70
60
50
40
30
20
10
3.273
Onset Y=35.1840 mW
Onset X=158.01 °C
Onset Y=27.9006 mW
Onset X=158.35 °C
102.8
120
140
160
180
200
220
242
Temperature (°C)

FIG.12

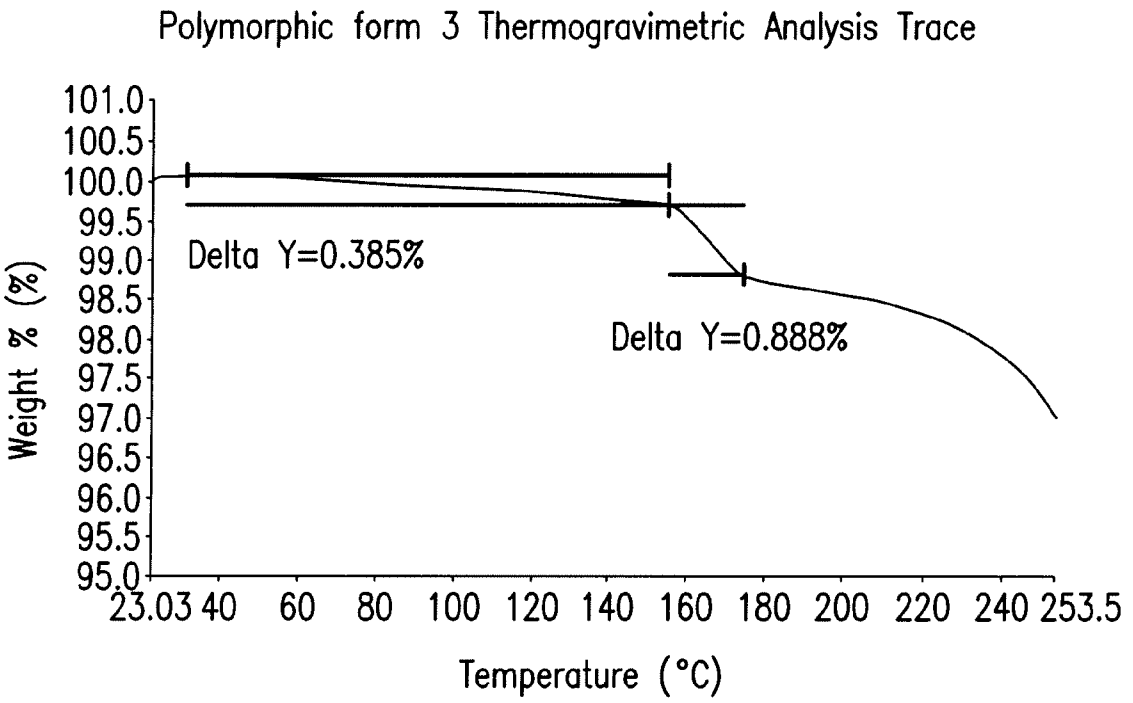

Polymorphic form 3 Thermogravimetric Analysis Trace
Weight % (%)
101.0
100.5
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
Delta Y=0.385%
Delta Y=0.888%
23.03 40 60 80 100 120 140 160 180 200 220 240 253.5
Temperature (°C)

FIG. 13

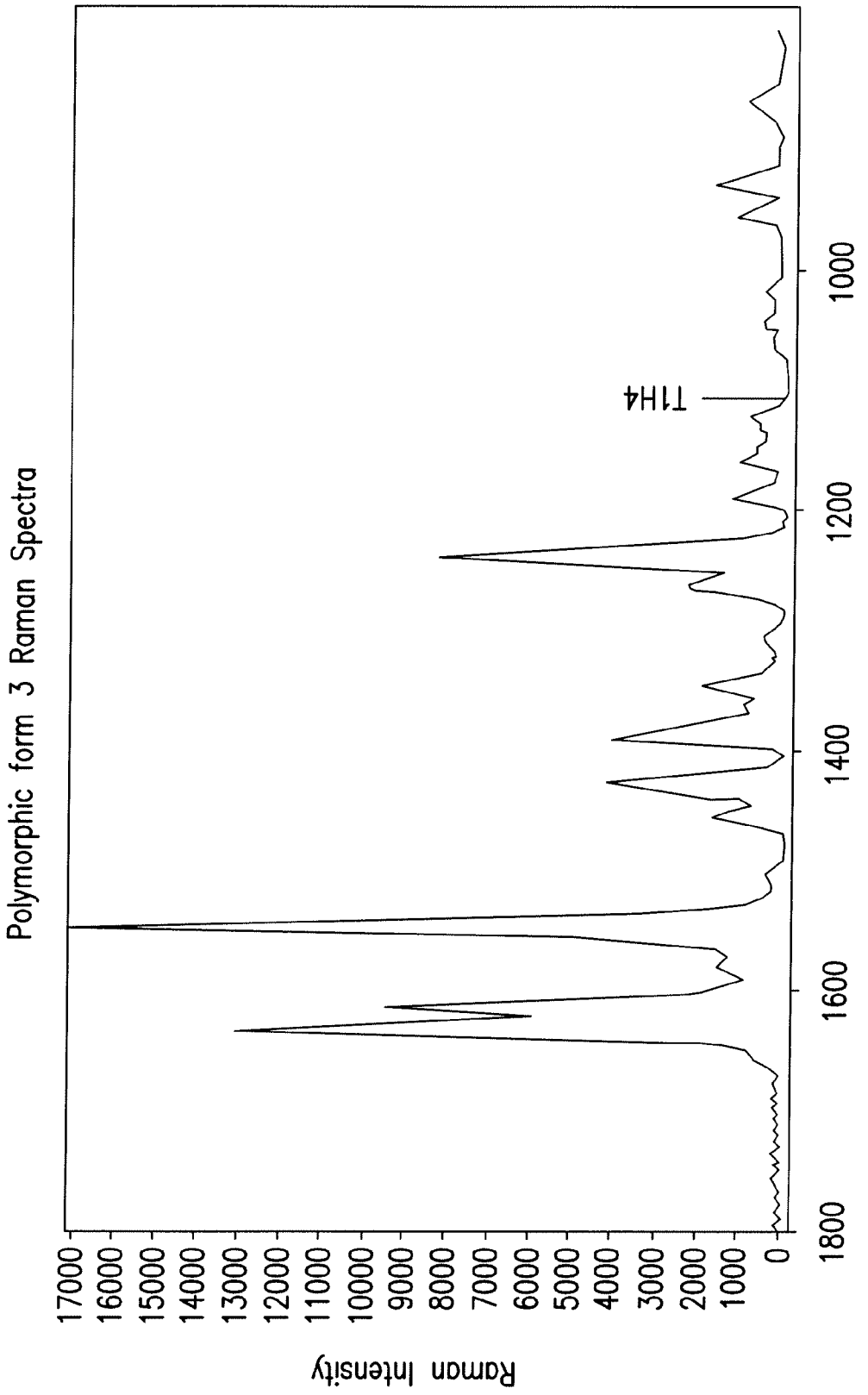

Polymorphic form 3 Raman Spectra
Raman Intensity
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1800
1600
1400
1200
1000
Raman shift (cm-1)
T1H4

FIG.14

Polymorphic form 3 Optical Microscope Images

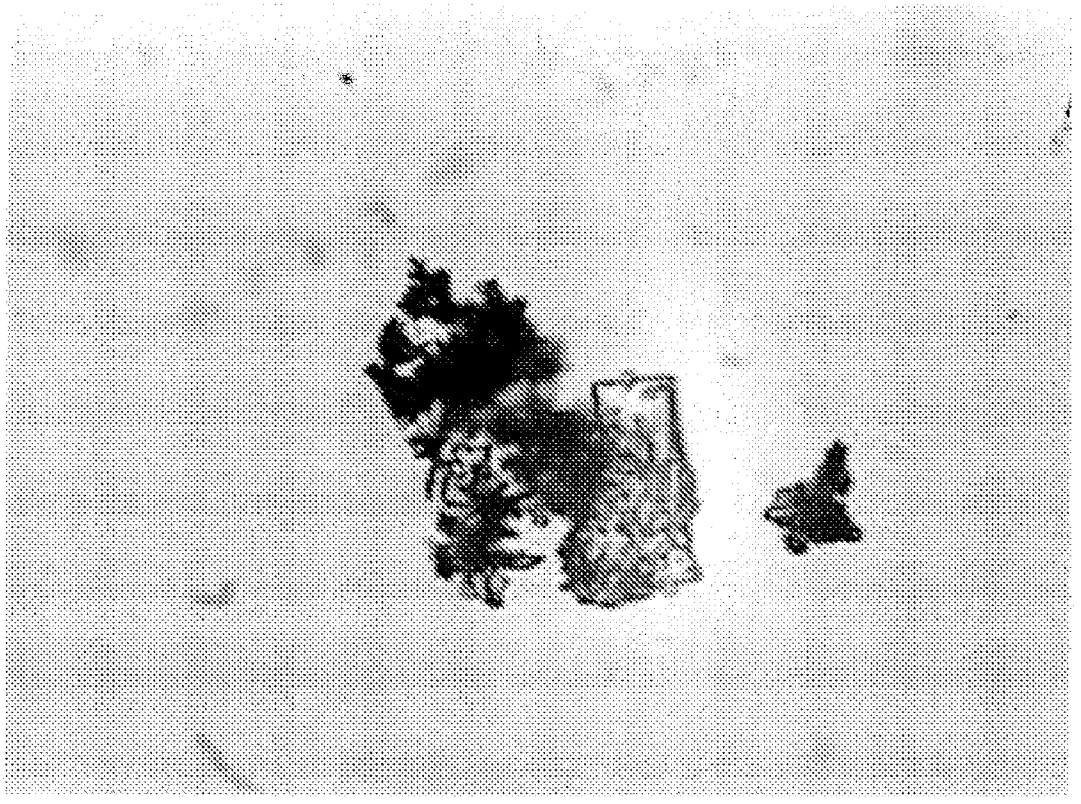


FIG. 15

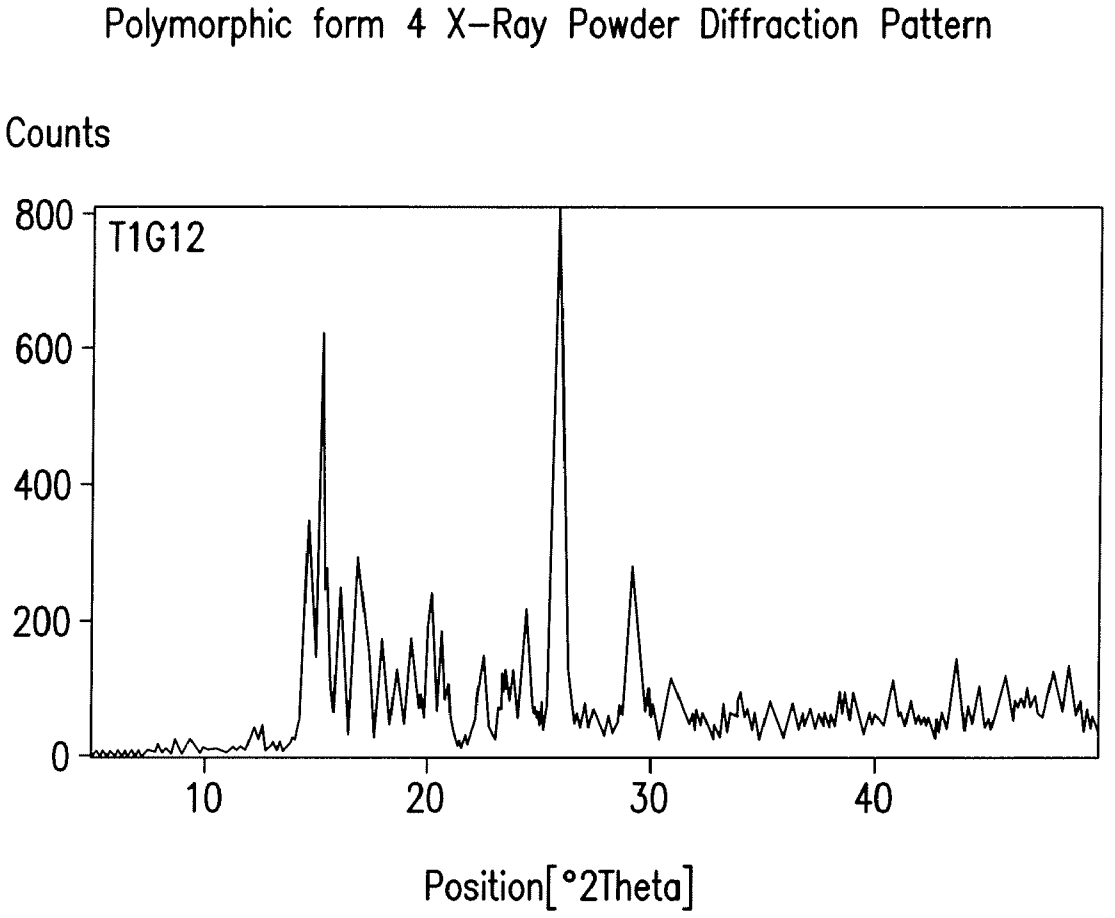

Polymorphic form 4 X-Ray Powder Diffraction Pattern
Counts
800
600
400
200
0
T1G12
10
20
30
40
Position[°2Theta]

FIG. 16

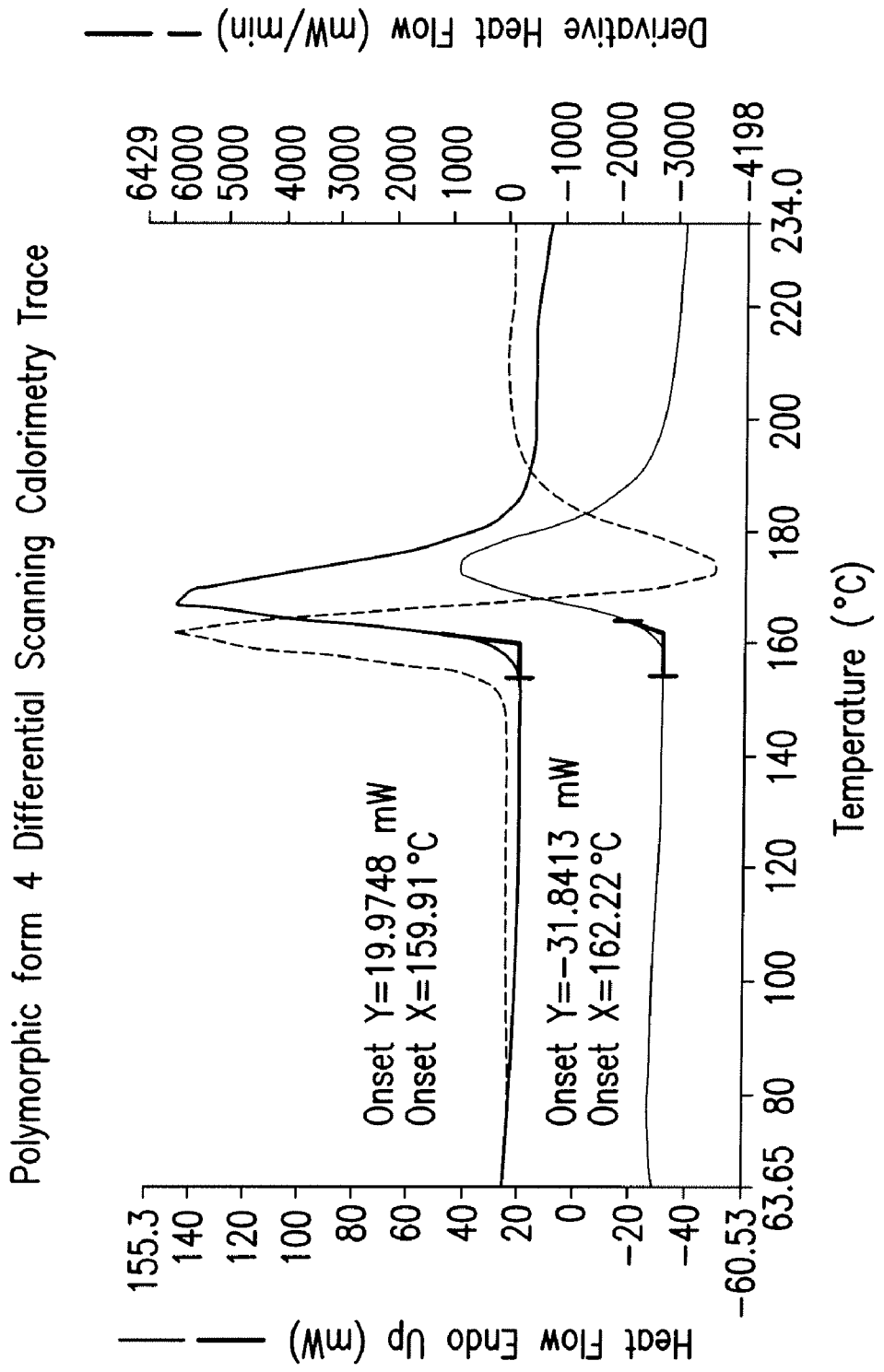

Polymorphic form 4 Differential Scanning Calorimetry Trace
Heat Flow Endo Up (mW)
Derivative Heat Flow (mW/min)
Temperature (°C)
Onset Y=19.9748 mW
Onset X=159.91 °C
Onset Y=−31.8413 mW
Onset X=162.22 °C
155.3
140
120
100
80
60
40
20
0
−20
−40
−60.53
6429
6000
5000
4000
3000
2000
1000
0
−1000
−2000
−3000
−4198
63.65
80
100
120
140
160
180
200
220
234.0

FIG. 17

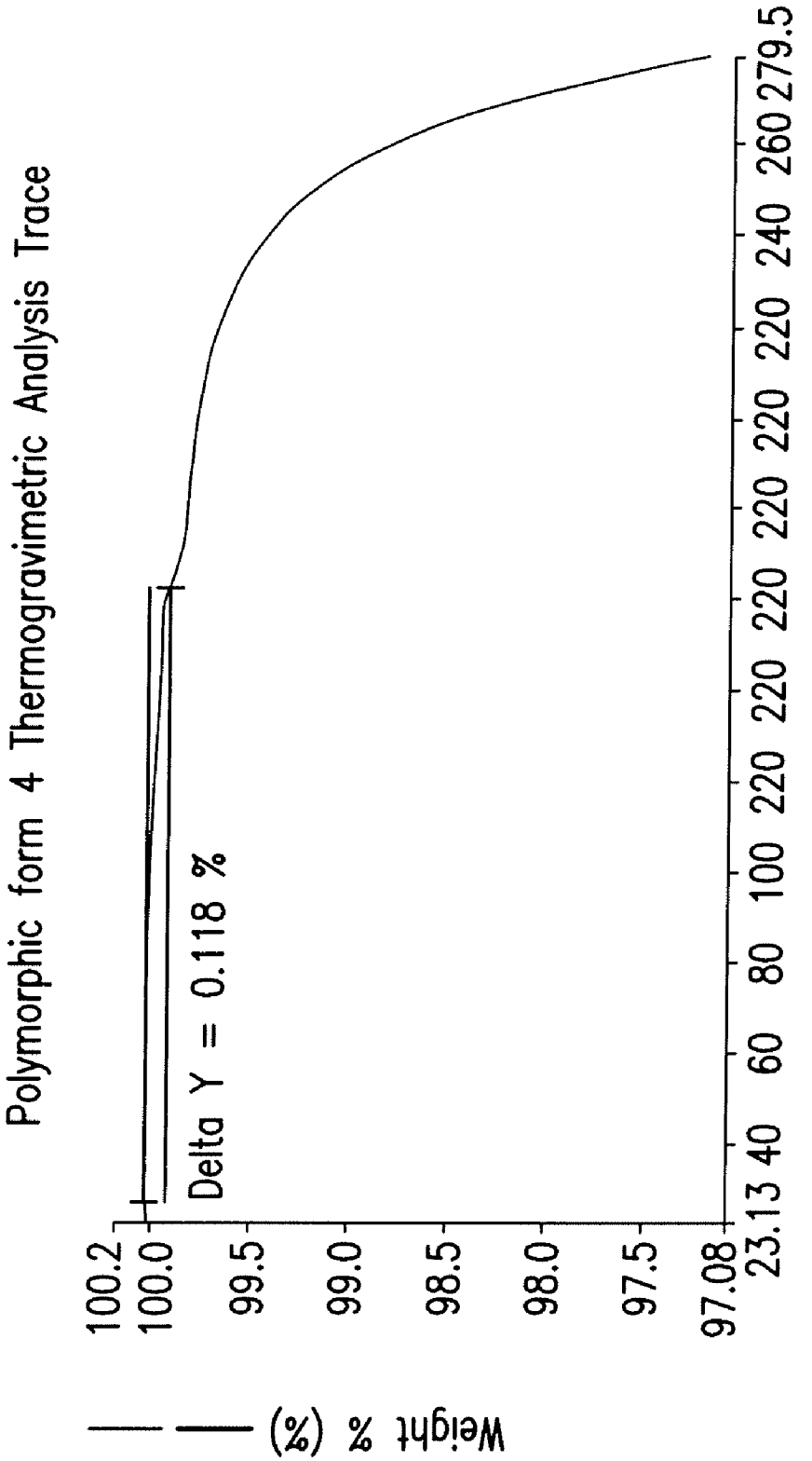

Polymorphic form 4 Thermogravimetric Analysis Trace
Delta Y = 0.118 %
Weight % (%)
Temperature (°C)
100.2
100.0
99.5
99.0
98.5
98.0
97.5
97.08
23.13
40
60
80
100
220
220
220
220
220
240
260
279.5

FIG. 18

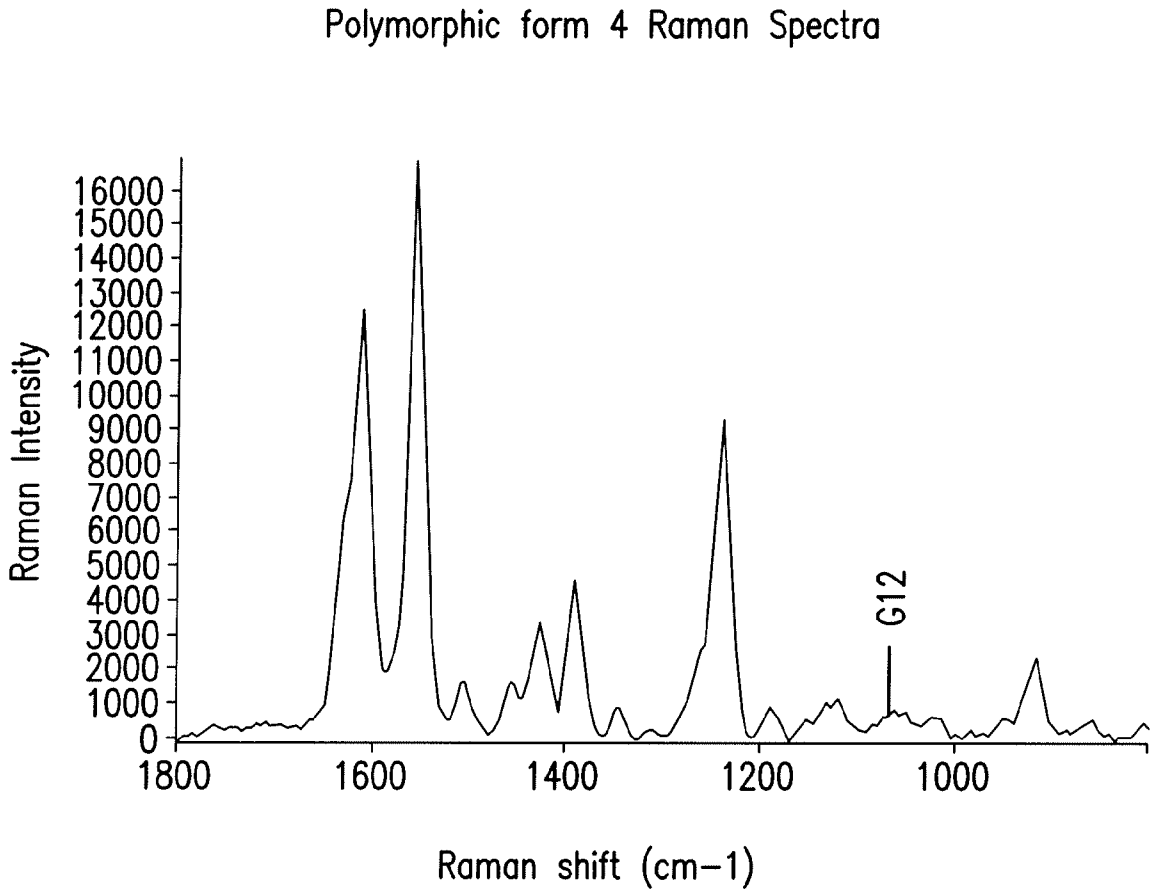

Polymorphic form 4 Raman Spectra
Raman Intensity
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1800
1600
1400
1200
1000
G12
Raman shift (cm−1)

FIG.19

Polymorphic form 4 Optical Microscope Images

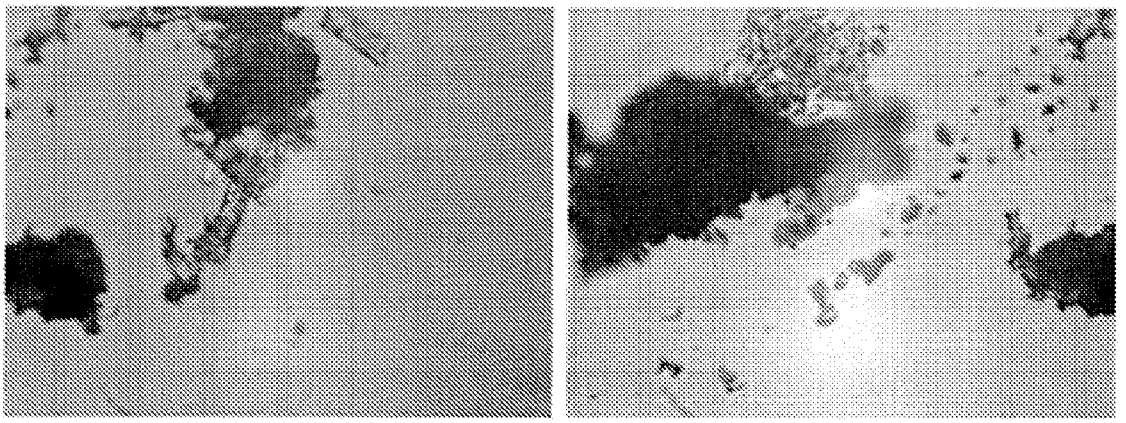


FIG.20

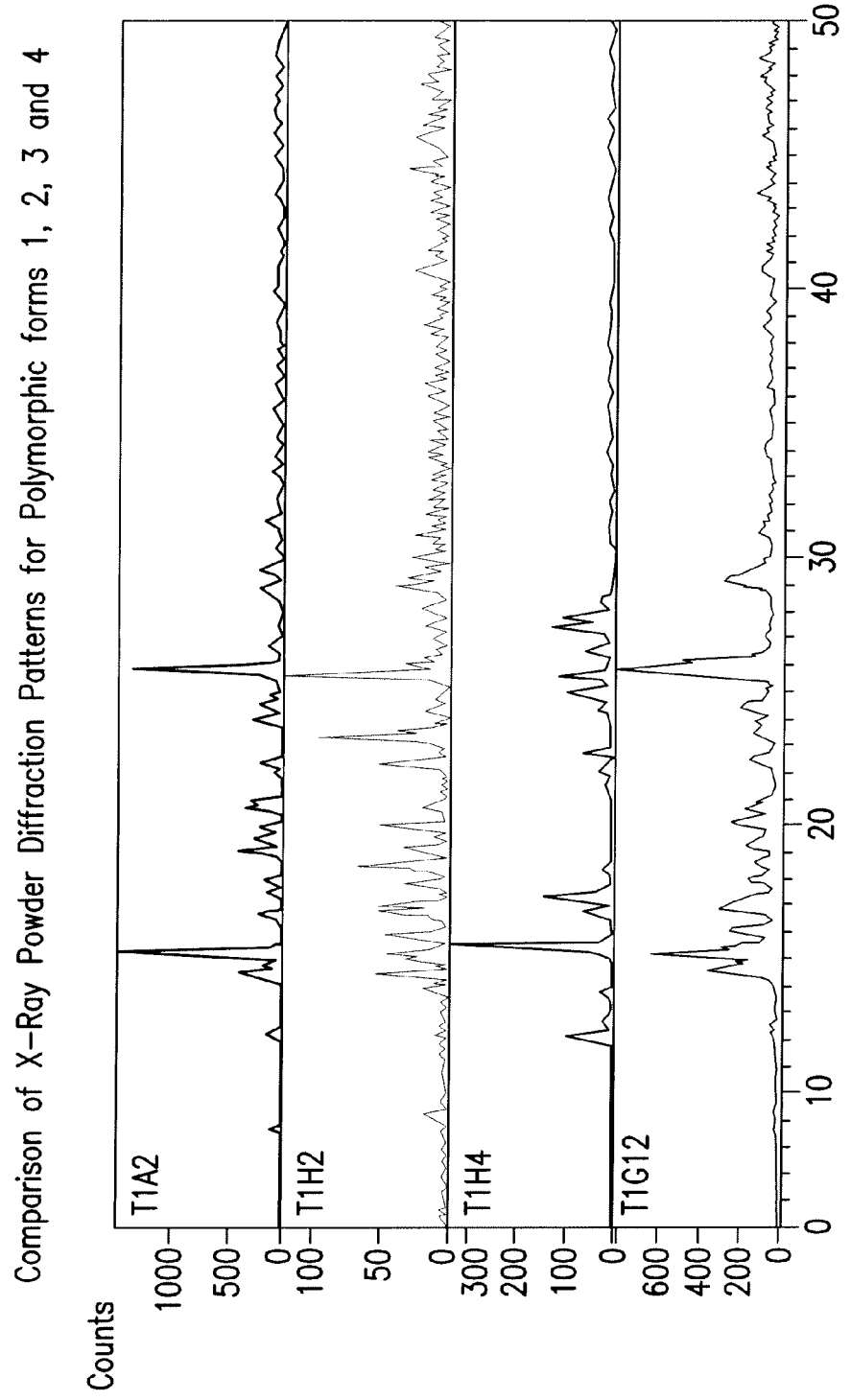

Comparison of X-Ray Powder Diffraction Patterns for Polymorphic forms 1, 2, 3 and 4
Counts
T1A2
T1H2
T1H4
T1G12
1000
500
0
100
50
0
300
200
100
0
600
400
200
0
0
10
20
30
40
50
Position [°2Theta]

FIG.21

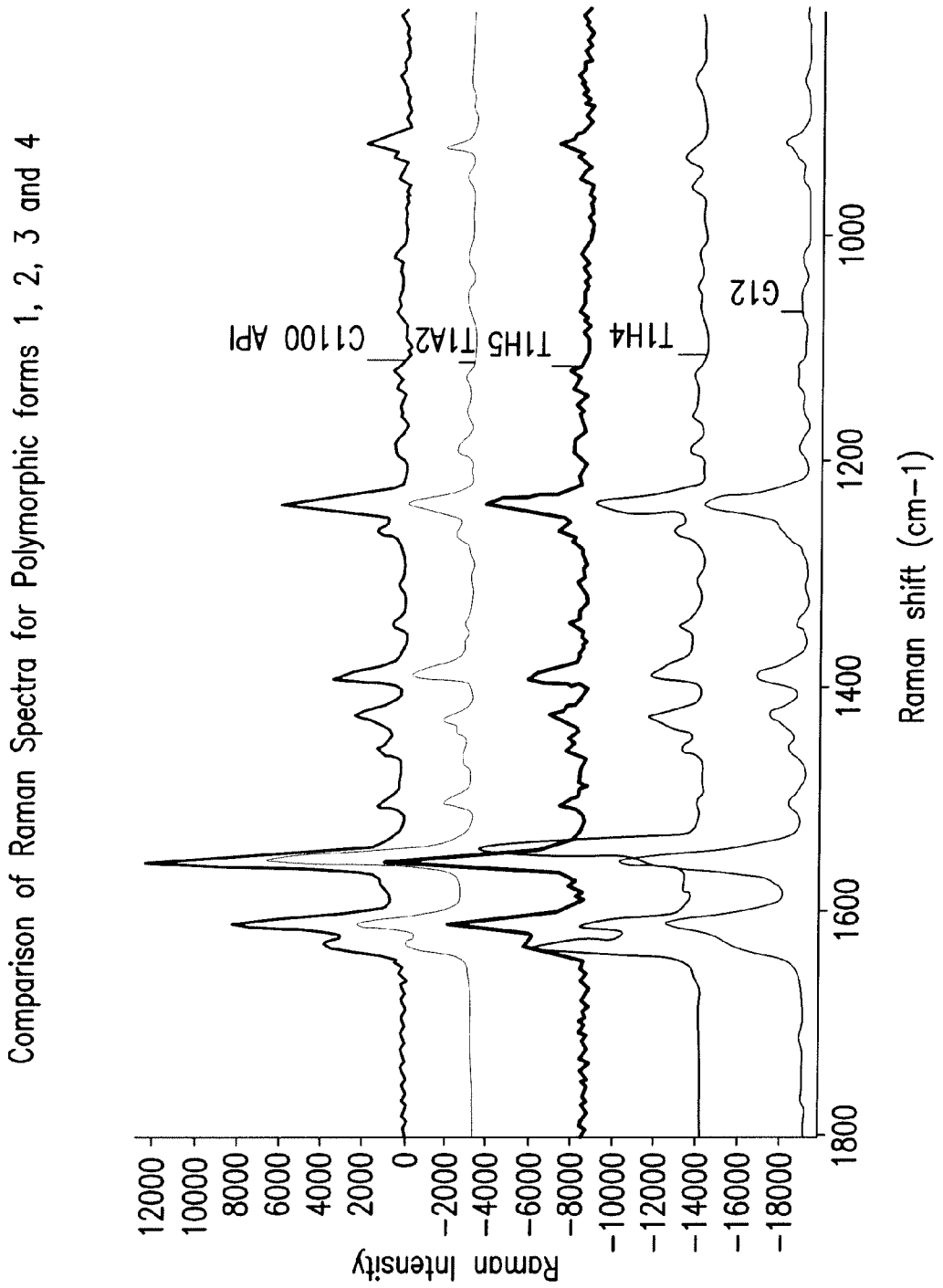

Comparison of Raman Spectra for Polymorphic forms 1, 2, 3 and 4
Raman Intensity
12000
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
-12000
-14000
-16000
-18000
1800
1600
1400
1200
1000
Raman shift (cm-1)
C1100 API
T1H5 T1A2
T1H4
G12

FIG.22

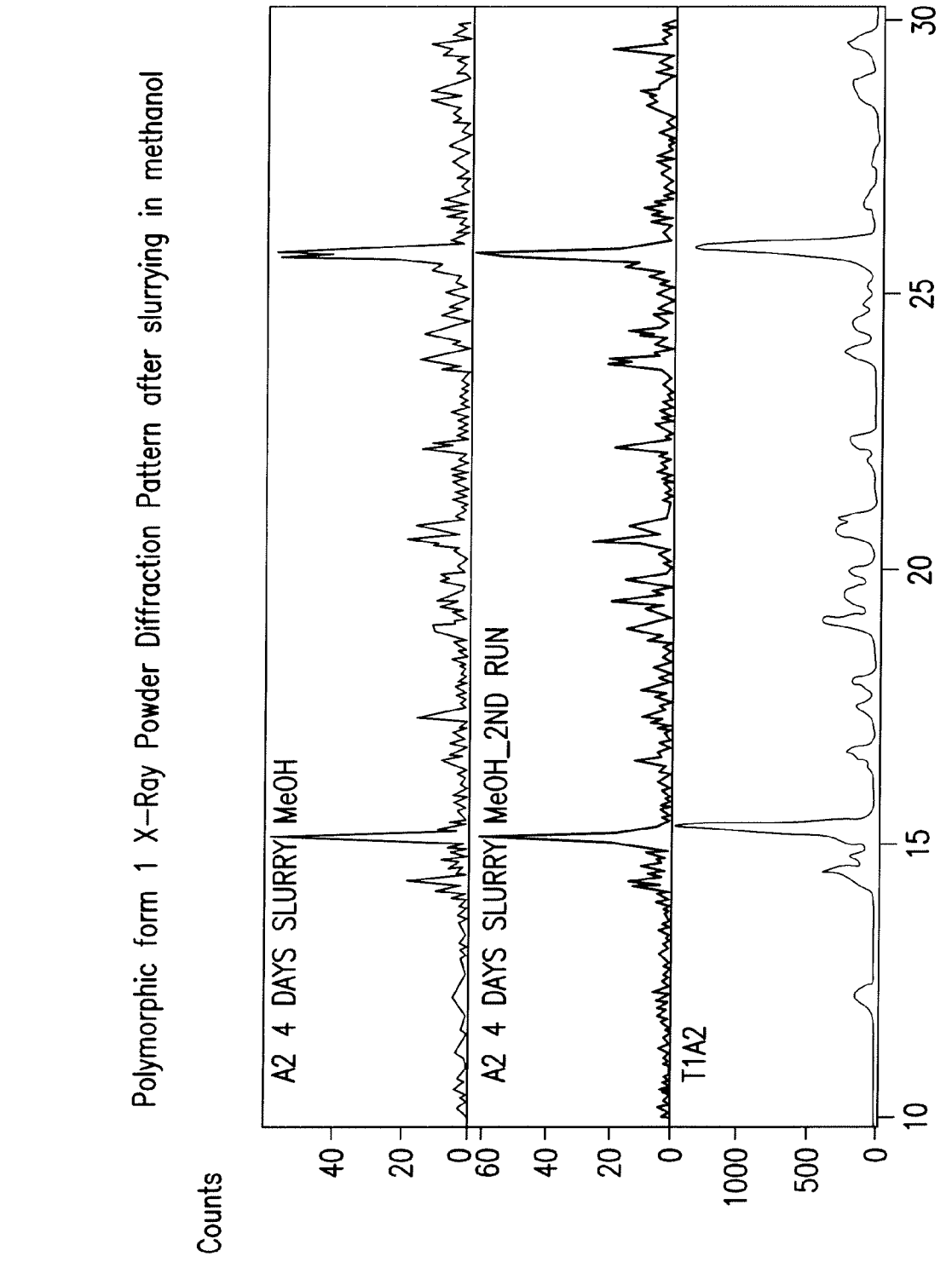

Polymorphic form 1 X-Ray Powder Diffraction Pattern after slurrying in methanol
Counts
A2 4 DAYS SLURRY MeOH
A2 4 DAYS SLURRY MeOH_2ND RUN
T1A2
40
20
0
60
40
20
0
1000
500
0
10
15
20
25
30
Position [°2Theta]

FIG.23

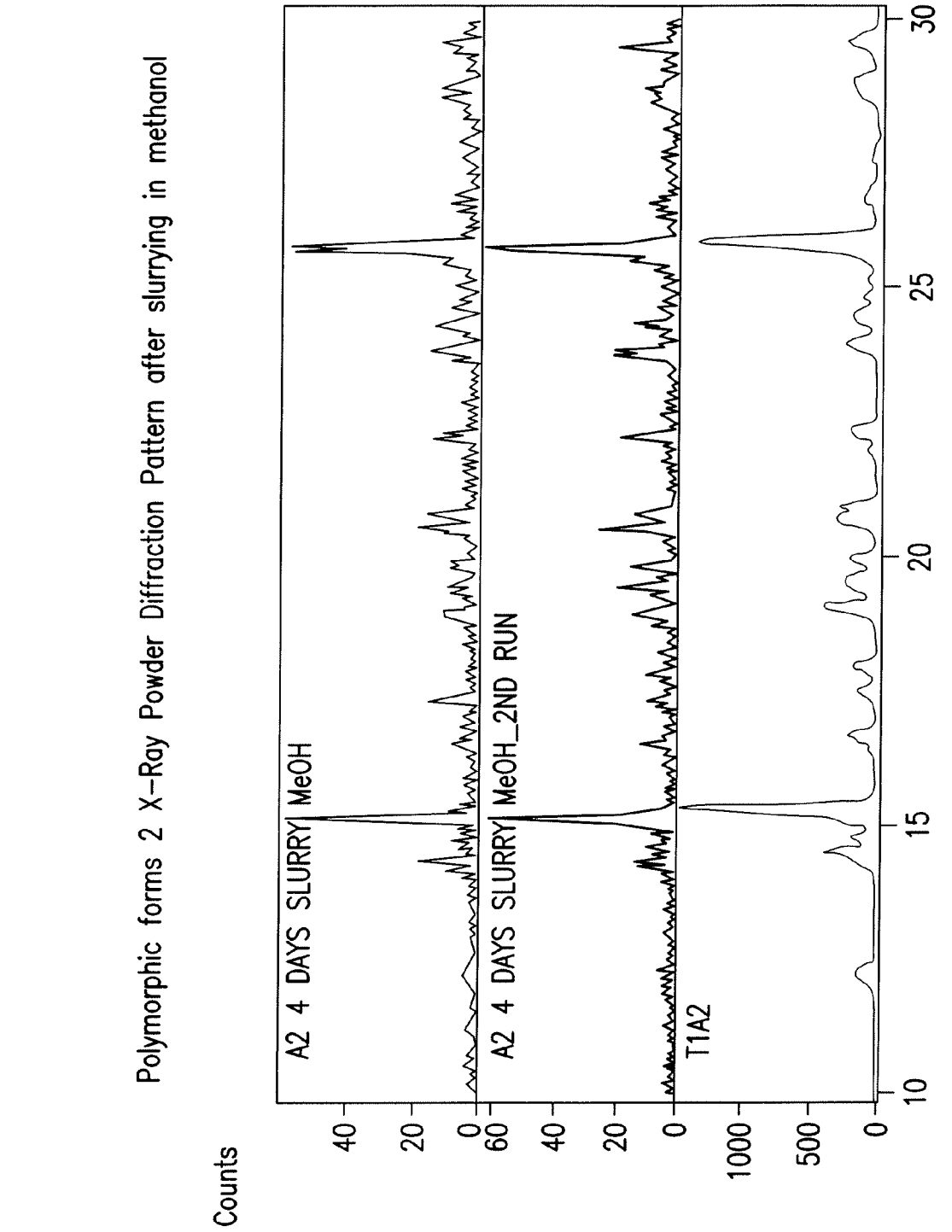

Polymorphic forms 2 X-Ray Powder Diffraction Pattern after slurrying in methanol
Counts
A2 4 DAYS SLURRY MeOH
A2 4 DAYS SLURRY MeOH_2ND RUN
T1A2
40
20
0
60
40
20
0
1000
500
0
10
15
20
25
30
Position [°2Theta]

FIG.24

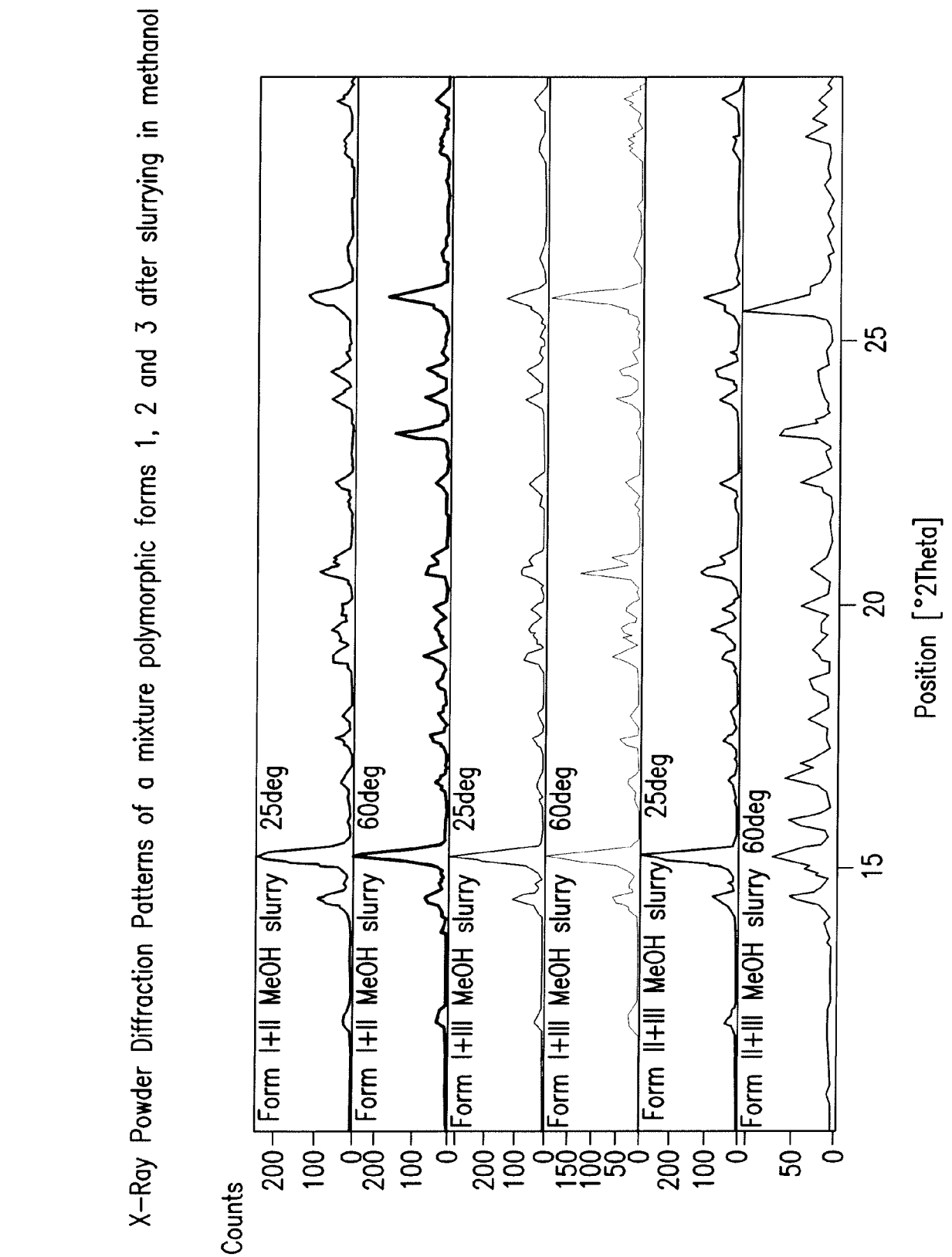

X-Ray Powder Diffraction Patterns of a mixture polymorphic forms 1, 2 and 3 after slurrying in methanol
Counts
Form I+II MeOH slurry 25deg
Form I+II MeOH slurry 60deg
Form I+III MeOH slurry 25deg
Form I+III MeOH slurry 60deg
Form II+III MeOH slurry 25deg
Form II+III MeOH slurry 60deg
Position [°2Theta]
15
20
25

FIG.25

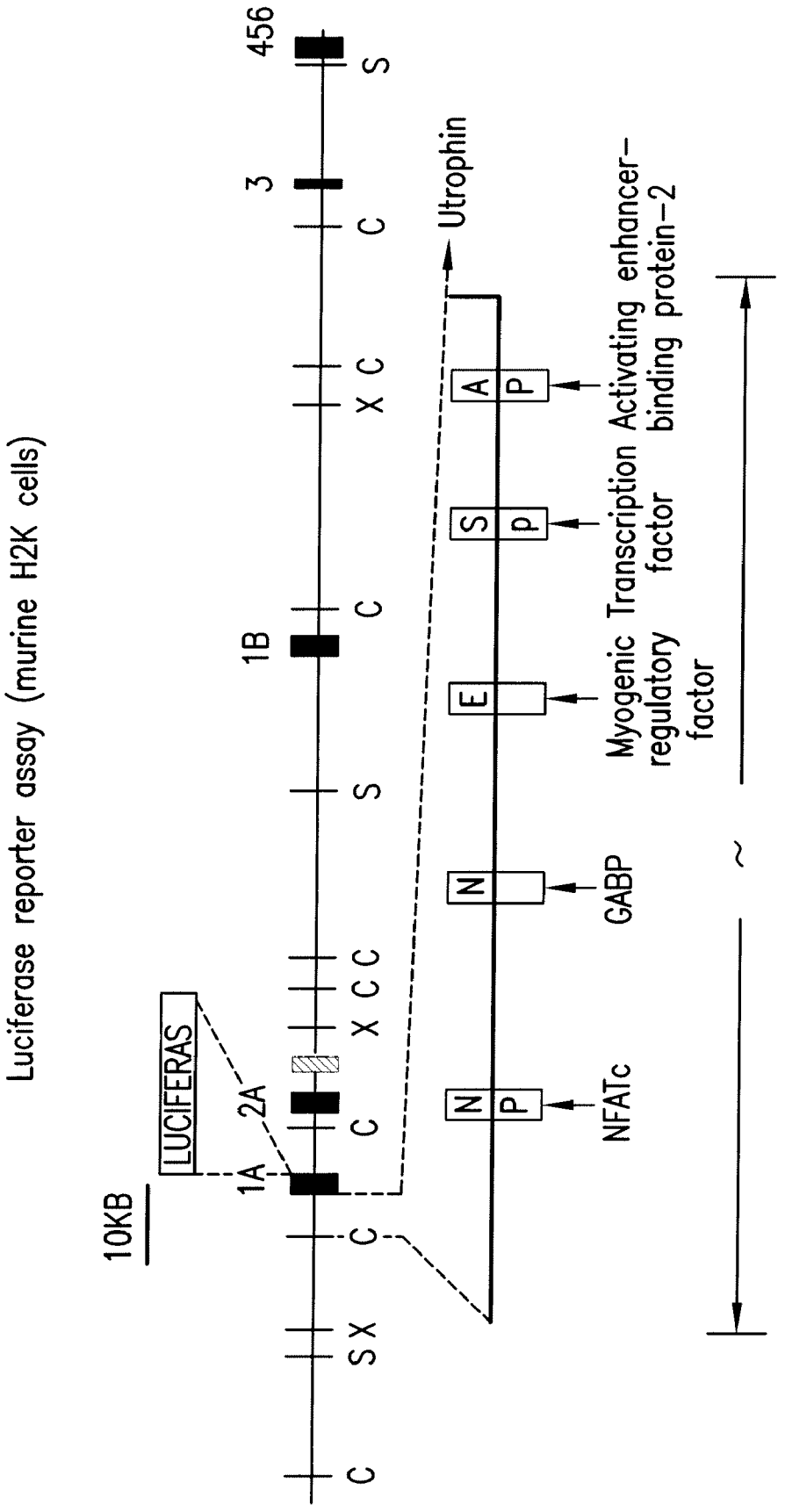
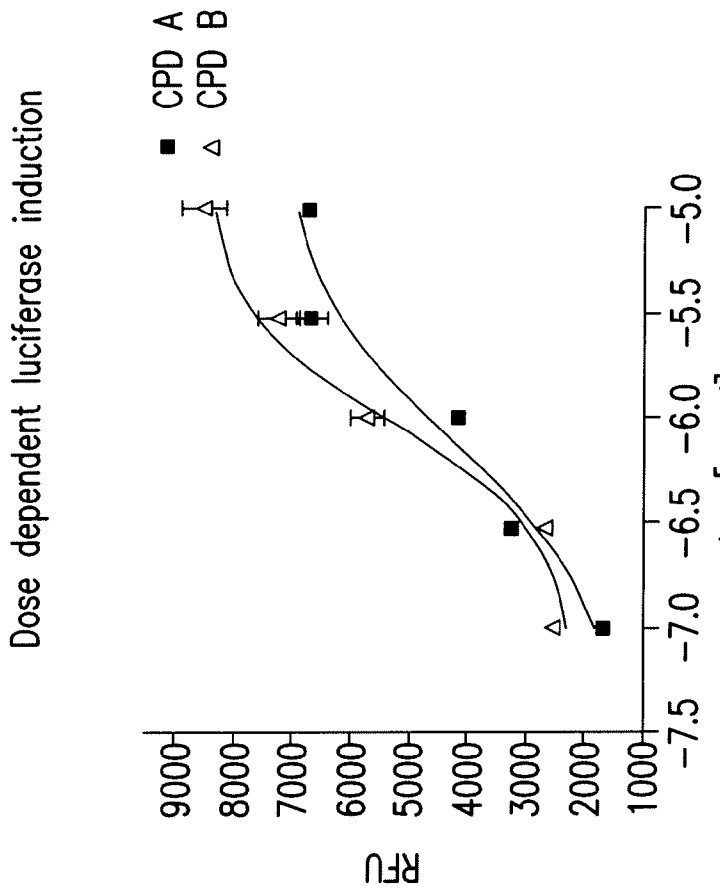

Luciferase reporter assay (murine H2K cells)
10KB
LUCIFERAS
1A
2A
1B
3
456
S
C
X
C
C
S
C
C
X
C
S
X
C
Utrophin
A
P
S
p
E
N
GABP
N
P
NFATc
Myogenic Transcription Activating enhancer-binding protein-2
regulatory factor
factor

FIG.26



	CPD A	CPD B
EC50	7.975e-007	9.532e-007

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

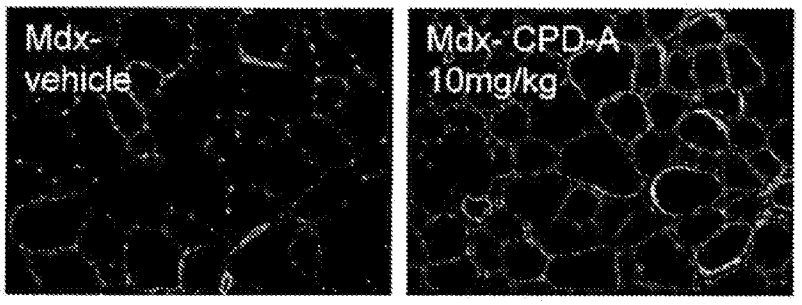

Mdx-
vehicle
Mdx- CPD-A
10mg/kg

FIG.28

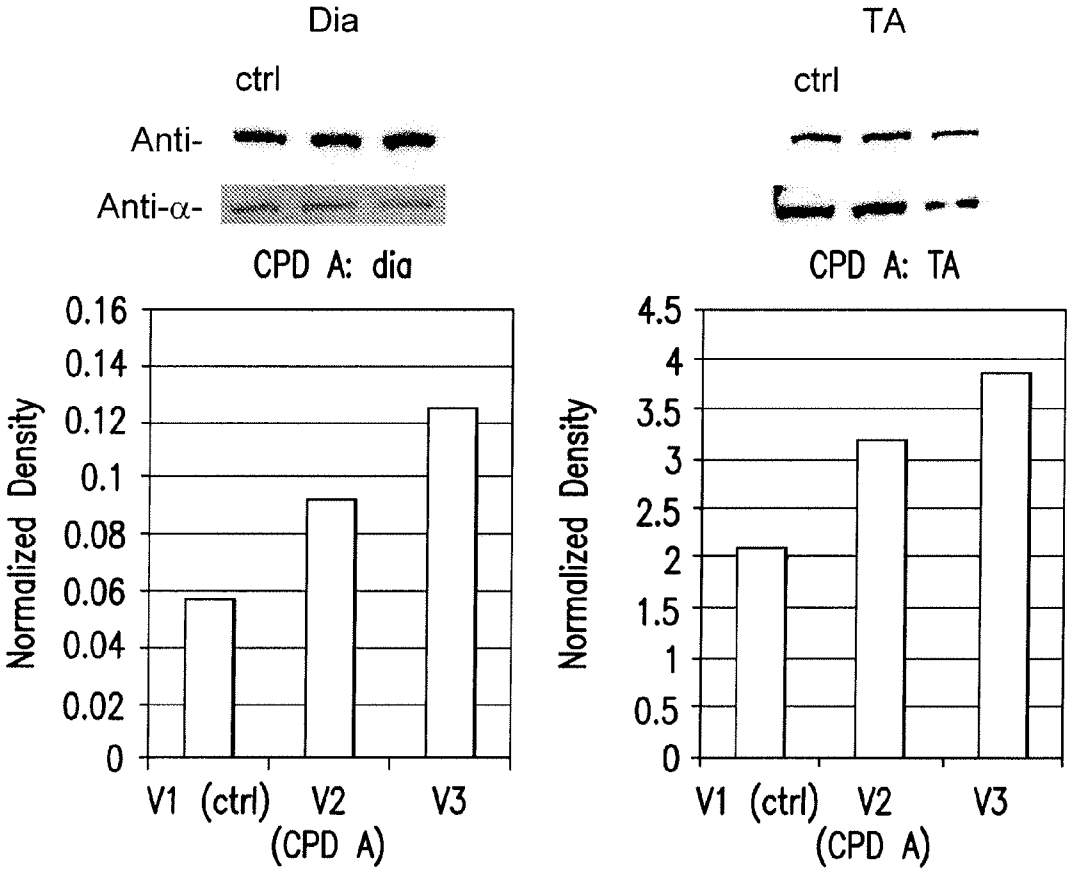

Dia
ctrl
Anti-
Anti-α-
CPD A: dia
Normalized Density
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
V1 (ctrl) V2 V3
(CPD A)
TA
ctrl
CPD A: TA
Normalized Density
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
V1 (ctrl) V2 V3
(CPD A)

FIG.29

TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

RELATED APPLICATION

[0001] Priority is claimed herein to British application GB0715937.9, filed Aug. 15, 2007, entitled "TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY." The above-referenced application is incorporated by reference herein in its entirety.

FIELD

[0002] Provided are polymorphic forms of a compound for the treatment of Duchenne muscular dystrophy.

BACKGROUND

[0003] 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 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 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.

[0004] 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 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.

[0005] 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)).

[0006] 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.

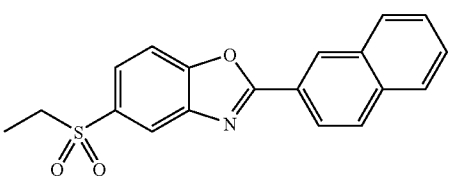
[0007] Pharmacological approaches for the treatment of muscular dystrophy differ from gene- and cell-based approaches in not being designed to deliver either the missing gene and/or protein. In general, the pharmacological strategies use drugs/molecules in an attempt to improve the phenotype by means 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.

[0008] 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 paralogue 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.

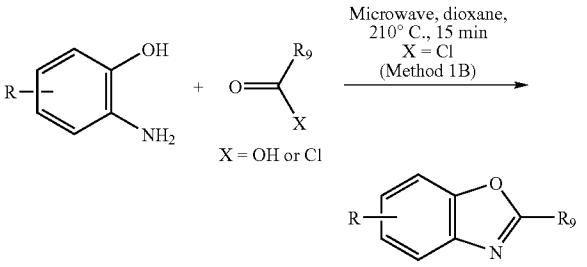
DESCRIPTION

[0009] It has been discovered by the applicants 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 2007/091106).

(I)



[0010] 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):



[0011] Method 1B is detailed on pages 67-68 in relation to 2-benzyl-5-nitrobenzo[d]oxazole as follows:

[0012] "Method 1B (Compounds I)

2-Benzyl-5-nitrobenzo[d]oxazole

[0013] To 2-amino-4-nitrophenol (300 mg, 1.95 mmol) in dioxane (2.5 mL) was added 2-phenylacetyl chloride (290 μL, 2.15 mmol) at room temperature. The reaction vessel was heated in the microwave at 210° C. for 15 min. After cooling, the mixture was slowly poured into 1M aqueous sodium hydroxide (50 mL), 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 165 mg (33%) of the title compound (LCMS RT=6.47 min, MH^+ 255.2)

[0014] ^{1}H 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)"

[0015] 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).

[0016] 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).

[0017] 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.

[0018] Accordingly, provided are polymorphs of the compound of formula I having advantageous properties and processes by which the polymorphs can be prepared.

[0019] In the following description, X-ray powder diffraction pattern peaks are given as °2θ and Raman spectra peaks are given as cm^{-1}.

[0020] 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±0.2.

[0021] 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±0.2.

[0022] 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±0.2.

[0023] 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±0.2.

[0024] 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±0.2, 16.7±0.2, 19.1±0.2 and 24.0±0.2.

[0025] 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±0.2, 18.5±0.2 and 23.3±0.2.

[0026] 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±0.2, 17.4±0.2, 22.7±0.2, 25.0±0.2 and 26.5±0.2.

[0027] 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±0.2, 16.1±0.2, 17.0±0.2, 19.3±0.2 and 29.2±0.2.

[0028] The instant disclosure will now be described with reference to the accompanying drawings in which:

[0029] FIG. **1** shows the x-ray powder diffraction pattern for polymorphic form 1;

[0030] FIG. **2** shows the differential scanning calorimetry trace for polymorphic form 1;

[0031] FIG. **3** shows the thermogravimetric analysis trace for polymorphic form 1;

[0032] FIG. **4** shows the Raman spectra for polymorphic form 1;

[0033] FIG. **5** shows optical microscope images of polymorphic form 1;

[0034] FIG. **6** shows the x-ray powder diffraction pattern for polymorphic form 2;

[0035] FIG. **7** shows the differential scanning calorimetry trace for polymorphic form 2;

[0036] FIG. **8** shows the thermogravimetric analysis trace for polymorphic form 2;

[0037] FIG. **9** shows the raman spectra for polymorphic form 2;

[0038] FIG. **10** shows optical microscope images of polymorphic form 2;

[0039] FIG. **11** shows the x-ray powder diffraction pattern for polymorphic form 3;

[0040] FIG. **12** shows the differential scanning calorimetry trace for polymorphic form 3;

[0041] FIG. **13** shows the thermogravimetric analysis trace for polymorphic form 3;

[0042] FIG. **14** shows the raman spectra for polymorphic form 3;

[0043] FIG. **15** shows optical microscope images of polymorphic form 3;

[0044] FIG. **16** shows the x-ray powder diffraction pattern for polymorphic form 4;

[0045] FIG. **17** shows the differential scanning calorimetry trace for polymorphic form 4;

[0046] FIG. **18** shows the thermogravimetric analysis trace for polymorphic form 4;

[0047] FIG. **19** shows the raman spectra for polymorphic form 4;

[0048] FIG. **20** shows optical microscope images of polymorphic form 4;

[0049] FIG. **21** shows a comparison of the x-ray powder diffraction patterns for polymorphic forms 1, 2, 3 and 4;

[0050] FIG. **22** shows a comparison of Raman spectra for polymorphic forms 1, 2, 3 and 4;

[0051] FIG. **23**: shows the x-ray powder diffraction pattern of polymorphic form 1 before and after slurrying in methanol;

[0052] FIG. **24**: shows the x-ray powder diffraction pattern of polymorphic form 2 before and after slurrying in methanol; and

[0053] FIG. **25**: shows the x-ray powder diffraction pattern of a mixture of polymorphic forms 1, 2 and 3 after slurrying in methanol.

[0054] FIG. **26**: show a diagram of an immortalized mdx mouse H2K cell line that has been stably transfected with a plasmid containing ≈5 kb fragment of the Utrophin A promoter including the first untranslated exon linked to a luciferase reporter gene.

[0055] FIG. **27**: shows pharmacological dose response of compounds in the luciferase reporter assay.

[0056] FIG. **28**: shows an example of TA muscle sections stained with antibody specific for mouse utrophin.

[0057] FIG. **29**: shows increased levels of utrophin expression compared to control in mice exposed to CPD-A (V2 and V3).

[0058] In one embodiment, provided is the polymorphic form 1 having an x-ray powder diffraction pattern substantially in accordance with FIG. **1**.

[0059] In another embodiment, provided is the polymorphic form 1 having a differential scanning calorimetry trace substantially in accordance with FIG. **2**.

[0060] In another embodiment, provided is the polymorphic form 1 having a thermogravimetric analysis trace substantially in accordance with FIG. **3**.

[0061] In another embodiment, provided is the polymorphic form 1 having a raman spectra substantially in accordance with FIG. **4**.

[0062] In another embodiment, provided is the polymorphic form 2 having an x-ray powder diffraction pattern substantially in accordance with FIG. **6**.

[0063] In another embodiment, provided is the polymorphic form 2 having a differential scanning calorimetry trace substantially in accordance with FIG. **7**.

[0064] In another embodiment, provided is the polymorphic form 2 having a thermogravimetric analysis trace substantially in accordance with FIG. **8**.

[0065] In another embodiment, provided is the polymorphic form 2 having a raman spectra substantially in accordance with FIG. **9**.

[0066] In another embodiment, provided is the polymorphic form 3 having an x-ray powder diffraction pattern substantially in accordance with FIG. **11**.

[0067] In another embodiment, provided is the polymorphic form 3 having a differential scanning calorimetry trace substantially in accordance with FIG. **12**.

[0068] In another embodiment, provided is the polymorphic form 3 having a thermogravimetric analysis trace substantially in accordance with FIG. **13**.

[0069] In another embodiment, provided is the polymorphic form 3 having a raman spectra substantially in accordance with FIG. **14**.

[0070] In another embodiment, provided is the polymorphic form 4 having an x-ray powder diffraction pattern substantially in accordance with FIG. **16**.

[0071] In another embodiment, provided is the polymorphic form 4 having a differential scanning calorimetry trace substantially in accordance with FIG. **17**.

[0072] In another embodiment, provided is the polymorphic form 4 having a thermogravimetric analysis trace substantially in accordance with FIG. **18**.

[0073] In another embodiment, provided is the polymorphic form 4 having a raman spectra substantially in accordance with FIG. **19**.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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 only polymorphic form.

[0080] 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.

[0081] 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.

[0082] Also provided are processes for making each of polymorphic forms 1, 2, 3 and 4.

[0083] In one embodiment there is provided a process for synthesising polymorphic form 1 comprising the steps of:

[0084] (i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding IPA until a solid product forms wherein the ratio of acetone:IPA is 20:80; or

[0085] dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in EtOAc and then adding IPA until a solid product forms wherein the ratio of EtOAc:IPA is 40:60; or

[0086] dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in DMF and then adding IPA until a solid product forms wherein the ratio of DMF:IPA is 40:60; or

[0087] dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in acetone and then adding EtOH until a solid product forms wherein the ratio of acetone:EtOH is 40:60; or

[0088] 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

[0089] and then

[0090] (ii) separating the solid product.

[0091] In one embodiment there is provided a process for synthesising polymorphic form 2 comprising the steps of:

[0092] (i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding IPA until a solid product forms wherein the ration of xylene: IPA is either 20:80 or 80:20;

[0093] and then

[0094] (ii) separating the solid product.

[0095] In one embodiment there is provided a process for synthesising polymorphic form 3 comprising the steps of:

[0096] (i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in xylene and then adding IPA until a solid product forms wherein the ratio of xylene:IPA is 60:40;

[0097] and then

[0098] (ii) separating the solid product.

[0099] In one embodiment there is provided a process for synthesising polymorphic form 4 comprising the steps of:

[0100] (i) dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole in DMF;

[0101] and then

[0102] (ii) removing the DMF by evaporation to form a solid product.

[0103] 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.

[0104] It has been found that polymorphic form 1 exhibits increased stability over previously 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.

[0105] In this regard it has been discovered that polymorphic form 1 retains its structure before and after slurrying in methanol for four days at 25° C.

[0106] In contrast, after slurrying in methanol in a similar manner polymorphic form 2 is converted into polymorphic form 1, and mixtures of polymorphoic forms 1, 2 and 3 are also converted into polymorphic form 1.

[0107] 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.

[0108] 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 the polymorphic form of the compound of formula I in admixture with a pharmaceutically acceptable diluent or carrier.

[0109] 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:

[0110] for inhalation compositions—coarse lactose;

[0111] 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;

[0112] for suppositories—natural or hardened oils or waxes.

[0113] 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 10 μm. 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 compositions may be formulated in sustained release form.

[0114] The content of the polymorphic form of the compound of formula I in a pharmaceutical composition is generally about 0.01-about 99.9 wt %, in one embodiment about 0.1-about 50 wt %, relative to the entire preparation.

[0115] 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.

[0116] 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.

[0117] 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.

1. Luciferase Reporter Assay (Murine H2K Cells)

[0118] The cell line used for the screen is an immortalized mdx mouse H2K cell line that has been stably transfected with a plasmid containing 5 kb fragment of the Utrophin A promoter including the first untranslated exon linked to a luciferase reporter gene (see FIG. **26**).

[0119] 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.

[0120] Examples of pharmacological dose response of compounds in the assay is shown in FIG. **27**.

2. Mdx Mouse

[0121] 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 the ability to increase the levels of utrophin protein in dystrophin deficient muscle when compared to vehicle only dosed control animals.

[0122] There were two animals injected with 10 mg/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 overall increases in utrophin levels).

[0123] FIG. **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.

[0124] Muscles from the above treated mice were also excised and processed for Western blotting and stained with specific antibodies (see FIG. **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.

[0125] 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 demonstrates that any increase of utrophin levels over three fold has significant functional effects on dystrophin deficient muscle.

[0126] The H2K/mdx/Utro A Reporter Cell Line Maintenance

[0127] The H2K/mdx/Utro A reporter cell line was passaged twice a week until ≦30% confluent. The cells were grown at 33° C. in the presence of 10% CO_2

[0128] To remove the myoblasts for platting, they were incubated with Trypsin/EDTA until the monolayer started to detach.

[0129] Growth Medium

[0130] DMEM Gibco 41966

[0131] 20% FCS

[0132] 1% Pen/Strep

[0133] 1% glutamine

[0134] 10 mls Chick embryo extract

[0135] Interferon (1276 905 Roche) Add fresh 10 μl/50 mls medium

Luciferase Assay for 96 Well Plates

[0136] 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 μl normal growth medium. The plates were then incubated at 33° C. in the presence of 10% CO_2 for 24 hrs.

[0137] Compounds were dosed by adding 10 μl of diluted compound to each well giving a final concentration of 10 μM. The plates were then incubated for a further 48 hrs

[0138] 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).

Compound Storage

[0139] Compounds for screening were stored at −20° C. as 10 mM stocks in 100% DMSO until required.

Injection of Mdx Mice with Compounds

[0140] Mdx from a breeding colony were selected for testing. Mice were injected daily with either vehicle or up to 50 mg/kg of compound using the intreperitoneal route (ip). Mice were weighed and compounds diluted in 5% DMSO, 0.1% tween in PBS.

[0141] Mice were sacrificed by cervical dislocation at desired time points, and muscles excised for analysis

[0142] Muscle Analysis

Immunohistochemistry

[0143] Tissues for sectioning were dissected, immersed in OCT (Bright Cryo-M-Bed) and frozen on liquid nitrogen cooled isopentane. Unfixed 8 μM cryosections were cut on a Bright Cryostat, and stored at −80° C.

[0144] In readiness for staining, sections were blocked in 5% foetal 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 5 mins in PBS. Secondary antibodies also diluted in blocking reagent, were incubated for 1 hr in the dark in a humid chamber. Finally sections were washed three times 5 mins in PBS and coverslip Mounted with hydromount. Slides were analysed using a Leica fluorescent microscope.

Results

[0145] Biological activity as assessed using the luciferase reporter assay in murine H2K cells, and is classified as follows:

[0146] + Up to 200% relative to control

[0147] ++ Between 201% and 300% relative to control

[0148] +++ Between 301% and 400% relative to control

[0149] ++++ Above 401% relative to control

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

EXPERIMENTAL

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

[0150] 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:

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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 process through the gas scrubber).

[0156] The methanesulfonic acid was then added dropwise over a period of 30 mins and relux was maintained until no further water was being collected in the Dean-Stark apparatus (approx 15 mins).

[0157] 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.

[0158] The resulting solution was then left at ambient temperature for 18 h, 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)

[0159] The product was then dried in a vacuum oven at 65° C. at a pressure of 10 mbar until constant weight was achieved (less than 0.5 g difference between consecutive measurements of mass which must be at least 1 h apart).

[0160] The product was obtained as a sandy-beige powder in a yield of 80%.

Characterisation:

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

[0161] LCMS RT=6.94 min, MH^+ 338.1;

[0162] ^{1}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);

[0163] MP=160-161° C.

Synthesis of Polymorphic Forms

1. Procedure

[0164] 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.

2. Thermodynamic Stability Testing

Slurrying Experiment (Single Form)

[0165] Approximately 10 mg of two polymorphic forms was slurried in 0.25 ml 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.

Slurrying Experiment (Mixed Forms)

[0166] Approximately 10 mg of a mixture of polymorphic forms were slurried together in 0.25 ml 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 powder X-ray diffraction.

3. Analytical Techniques

3.1 X-Ray Powder Diffraction (XRPD)

[0167] Approximately 2 mg of sample was gently compressed on the XRPD zero back ground single 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
Tube current: 40 mA
Wavelength alpha1: 1.5406 A
Wavelength alpha2: 1.5444 A
Start angle [2θ]: 5
End angle [2θ]: 35
Time per step: 2.5 seconds
Scan step size: 0.06

3.2 Differential Scanning Calorimetry

[0168] 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 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 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

[0169] 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 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 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 Thermogravimetric Analysis

[0170] 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

Polymorphic Form 1

[0171] Polymorphic form 1 was prepared under the above conditions using following solvent combinations:

Good solvent	Anti-solvent	Ratio good solvent:anti-solvent
Acetone	IPA	20:80
EtOAc	IPA	40:60
DMF	IPA	40:60
Acetone	EtOH	40:60

[0172] Polymorphic form 1 gives an x-ray powder diffraction pattern according to FIG. **1** having the following peaks:

No.	Position. [°2Th.]	d-spacing [Å]	Relative Intensity [%]
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
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

-continued

No.	Position. [°2Th.]	d-spacing [Å]	Relative Intensity [%]
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
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
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
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
32	45.7704	1.98242	7.23

[0173] Polymorphic form 1 gives a differential scanning calorimetry trace according to FIG. **2**.

[0174] Polymorphic form 1 gives a thermogravimetric analysis trace according to FIG. **3**.

[0175] Polymorphic form 1 gives a raman spectra according to FIG. **4** having the following peaks:

No.	Position. [cm^{-1}]
1	1628.57
2	1611.21
3	1554.92
4	1508.12
5	1463.63
6	1429.89
7	1390.53
8	1362.14
9	1264.03
10	1237.83
11	1190.93
12	921.63

[0176] FIG. **5** shows optical microscope images of polymorphic form 1.

Polymorphic Form 2

[0177] Polymorphic form 2 was prepared under the above conditions using following solvent combinations:

Good solvent	Anti-solvent	Ratio good solvent:anti-solvent
Xylene	IPA	20:80
Xylene	IPA	80:200

[0178] Polymorphic form 2 gives an x-ray powder diffraction pattern according to FIG. **6** having the following peaks:

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

[0179] Polymorphic form 2 gives a differential scanning calorimetry trace according to FIG. **7**.

[0180] Polymorphic form 2 gives a thermogravimetric analysis trace according to FIG. **8**.

[0181] Polymorphic form 2 gives a raman spectra according to FIG. **9** having the following peaks:

No.	Position. [cm^{-1}]
1	1630.74
2	1611.54
3	1557.07
4	1507.80
5	1426.48
6	1393.55
7	1262.55
8	1237.64
9	918.36

[0182] FIG. **10** shows optical microscope images of polymorphic form 2.

Polymorphic Form 3

[0183] Polymorphic form 3 was prepared under the above conditions using following solvent combination:

Good solvent	Anti-solvent	Ratio good solvent:anti-solvent
Xylene	IPA	60:40

[0184] Polymorphic form 3 gives an x-ray powder diffraction pattern according to FIG. **11** having the following peaks:

No.	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
1	12.1430	7.28886	25.01
2	12.7134	6.96307	6.44
3	13.6600	6.48261	8.31
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
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
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
19	28.2812	3.15567	13.54
20	29.0800	3.07078	3.31

[0185] Polymorphic form 3 gives a differential scanning calorimetry trace according to FIG. **12**.

[0186] Polymorphic form 3 gives a thermogravimetric analysis trace according to FIG. **13**.

[0187] Polymorphic form 3 gives a raman spectra according to FIG. **14** having the following peaks:

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

[0188] FIG. **15** shows optical microscope images of polymorphic form 3.

Polymorphic Form 4

[0189] Polymorphic form 4 was prepared by dissolving 100 mg of the compound of formula I in DMF and then removing the solvent by evaporation.

Good solvent	Anti-solvent	Ratio good solvent:anti-solvent
DMF	—	—

[0190] Polymorphic form 4 gives an x-ray powder diffraction pattern according to FIG. **16** having the following peaks:

No.	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
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
10	20.6800	4.29518	24.48
11	22.4554	3.95944	17.33
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
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
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

[0191] Polymorphic form 4 gives a differential scanning calorimetry trace according to FIG. **17**.

[0192] Polymorphic form 4 gives a thermogravimetric analysis trace according to FIG. **18**.

[0193] Polymorphic form 4 gives a raman spectra according to FIG. **19** having the following peaks:

No.	Position. [cm^{-1}]
1	1611.74
2	1556.66
3	1505.46
4	1455.21
5	1426.26
6	1390.80
7	1344.56
8	1238.72
9	1187.49
10	1119.38
11	1061.06
12	916.21

[0194] FIG. **20** shows optical microscope images of polymorphic form 4.

Slurrying Experiments

1. Polymorphic Form 1

[0195] Polymorphic form 1 was slurried in methanol and then the solid product isolated using the above slurrying 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 FIG. **23**. It can be seen that the diffraction pattern is the same before and after slurrying indicating that there is no change in the polymorphic form.

2. Polymorphic Form 2

[0196] Polymorphic form 2 was slurried in methanol and then the solid product isolated using the above slurrying 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 FIG. **24** together with the diffraction pattern for polymorphic form 1. It can be seen that the diffraction pattern of the product subsequent to slurrying is the same as that for polymorphic form 1, indicating that subsequent to slurrying, polymorphic form 1 has converted to polymorphic form 2.

3. Mixed Polymorphic Forms 1, 2 and 3.

[0197] The following mixtures of polymorphic forms were slurried in methanol according to the above slurrying experiment (mixed forms) both at 60° C. and at 25° C.:

Forms 1 and 2

Forms 1 and 3

Forms 2 and 3

[0198] The x-ray powder diffraction pattern of the solid products after slurrying were obtained. The spectra are illustrated by FIG. **25**.

[0199] As can be seen, at 25° C., after slurrying all mixtures converted into polymorphic form 1. However, after slurrying 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 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±0.2.

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±0.2.

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±0.2.

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±0.2.

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±0.2, 16.7±0.2, 19.1±0.2 and 24.0±0.2.

6. A polymorphic form of claim **1** having an x-ray powder diffraction pattern substantially in accordance with FIG. **1**.

7. A polymorphic form of claim **1** having a differential scanning calorimetry trace substantially in accordance with FIG. **2**.

8. A polymorphic form of claim **1** having a thermogravimetric analysis trace substantially in accordance with FIG. **3**.

9. A polymorphic form of claim **1** having a raman spectra substantially in accordance with FIG. **4**.

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 claim **1**.

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 of claim **1** as the only polymorphic form.

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±0.2, 18.5±0.2 and 23.3±0.2.

13. A polymorphic form of claim **12** having an x-ray powder diffraction pattern substantially in accordance with FIG. **6**.

14. A polymorphic form of claim **12** having a differential scanning calorimetry trace substantially in accordance with FIG. **7**.

15. A polymorphic form of claim **12** having a thermogravimetric analysis trace substantially in accordance with FIG. **8**.

16. A polymorphic form of claim **12** having a raman spectra substantially in accordance with FIG. **9**.

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 of claim **12**.

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 of claim **12** as the only polymorphic form.

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±0.2, 17.4±0.2, 22.7±0.2, 25.0±0.2 and 26.5±0.2.

20. A polymorphic form of claim **19** having an x-ray powder diffraction pattern substantially in accordance with FIG. **11**.

21. A polymorphic form of claim **19** having a differential scanning calorimetry trace substantially in accordance with FIG. **12**.

22. A polymorphic form of claim **19** having a thermogravimetric analysis trace substantially in accordance with FIG. **13**.

23. A polymorphic form of claim **19** having a raman spectra substantially in accordance with FIG. **14**.

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 of claim **19**.

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 of claim **19** as the only polymorphic form.

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 of claim **26** having an x-ray powder diffraction pattern substantially in accordance with FIG. **16**.

28. A polymorphic form of claim **26** having a differential scanning calorimetry trace substantially in accordance with FIG. **17**.

29. A polymorphic form of claim **26** having a thermogravimetric analysis trace substantially in accordance with FIG. **18**.

30. A polymorphic form of claim **26** having a raman spectra substantially in accordance with FIG. **19**.

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 of claim **26**.

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 of claim **26** 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 of claim **1** comprising the steps of:

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

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

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

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

dissolving 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d] oxazole in acetone at reflux 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 of claim **12** comprising the steps of:

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

and then

(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 of claim **19** comprising the steps of:

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

and then

(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 of claim **26** comprising the steps of:

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

and then

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

37. A method of treating Duchenne muscular dystrophy or Becker muscular dystrophy, comprising administering a polymorphic form of claim **1**.

38. A method of treating Duchenne muscular dystrophy or Becker muscular dystrophy, comprising administering a polymorphic form of claim **12**.

39. A method of treating Duchenne muscular dystrophy or Becker muscular dystrophy, comprising administering a polymorphic form of claim **19**.

40. A method of treating Duchenne muscular dystrophy or Becker muscular dystrophy, comprising administering a polymorphic form of claim **26**.

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