Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3048324 A1 2018/07/05

(21) 3 048 324

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2017/12/28
(87) Date publication PCT/PCT Publication Date: 2018/07/05
(85) Entrée phase nationale/National Entry: 2019/06/25
(86) N° demande PCT/PCT Application No.: IB 2017/001709
(87) N° publication PCT/PCT Publication No.: 2018/122606
(30) Priorité/Priority: 2016/12/28 (US62/439,533)

(51) Cl.Int./Int.Cl. *C07D 281/02* (2006.01),
A61K 31/554 (2006.01)

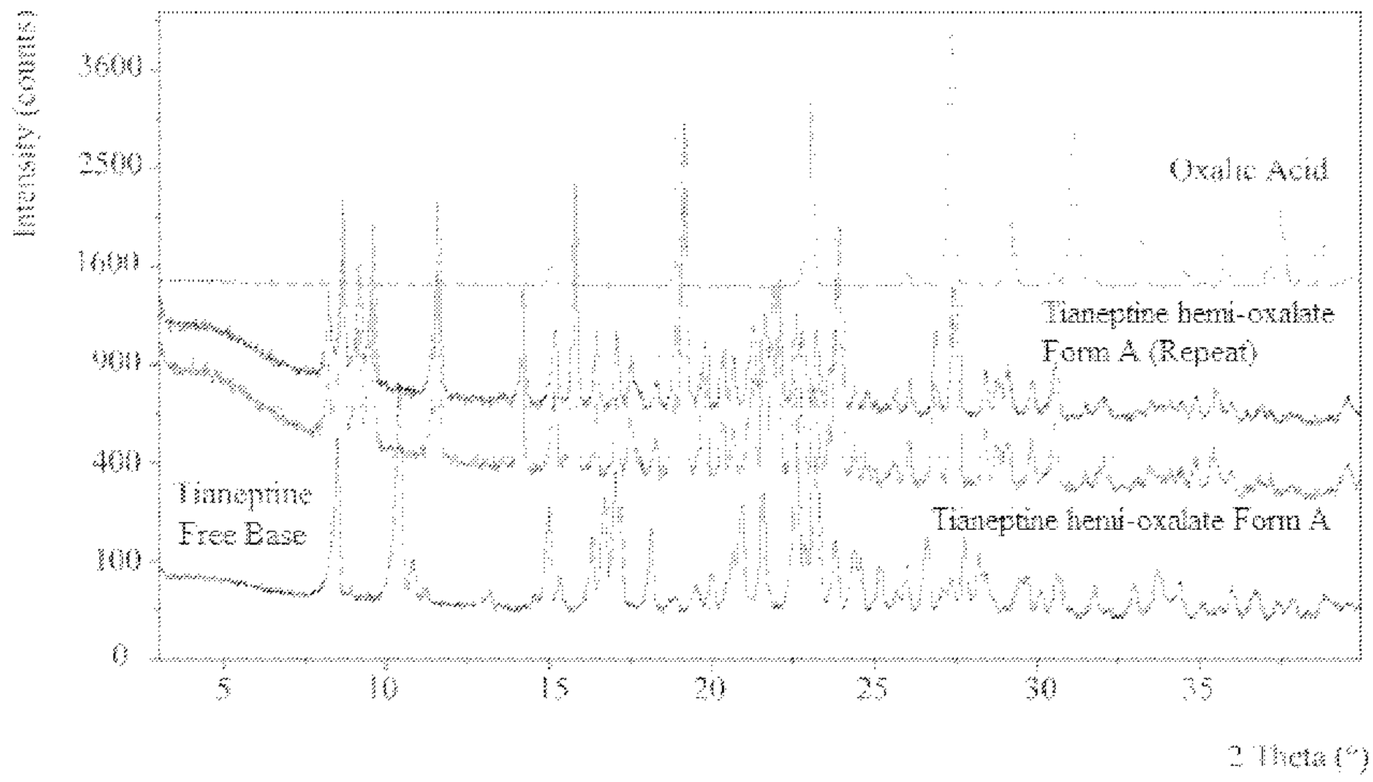
(71) Demandeur/Applicant:
TONIX PHARMA HOLDINGS LIMITED, BM

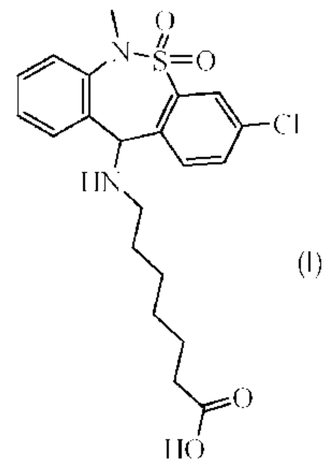
(72) Inventeurs/Inventors:
GIAFFREDA, STEFANO LUCA, IT;
MODENA, ENRICO, IT;
FABBRONI, SERENA, IT;
CHIARUCCI, MICHEL, IT;
EDGAR, MARK T., US

(74) Agent: SMART & BIGGAR

(54) Titre : SELS ET POLYMORPHES D'OXALATE DE TIANEPTINE
(54) Title: TIANEPTINE OXALATE SALTS AND POLYMORPHS

Figure 1





(I)

(57) Abrégé/Abstract:
Disclosed herein is an oxalate salt/co-crystal (tianeptine oxalate) of (RS)-7-(3-chloro-6- methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide (tianeptine) as shown in Formula (I).

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
05 July 2018 (05.07.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/122606 A1

(51) International Patent Classification:
C07D 281/02 (2006.01) *A61K 31/554* (2006.01)

(21) International Application Number:
PCT/IB2017/001709

(22) International Filing Date:
28 December 2017 (28.12.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/439,533 28 December 2016 (28.12.2016) US

(71) Applicant: **TONIX PHARMA HOLDINGS LIMITED** [IE/—]; Canon's Court, 22 Victoria Street, Hamilton HM 12 (BM).

(72) Inventors: **GIAFFREDA, Stefano, Luca**; Via Lombardia 10, 40139 Bologna (IT). **MODENA, Enrico**; Via San Vitale 74, 40125 Bologna (IT). **FABBRONI, Serena**; Via San Vitale Est 139, 40059 Medicina (IT). **CHIARUCCI, Michel**; Via Saffi 13, 40131 Bologna (IT). **EDGAR, Mark, T.**; 14090 Steeple Chase Row, Rancho Sante Fe, CA 92067 (US).

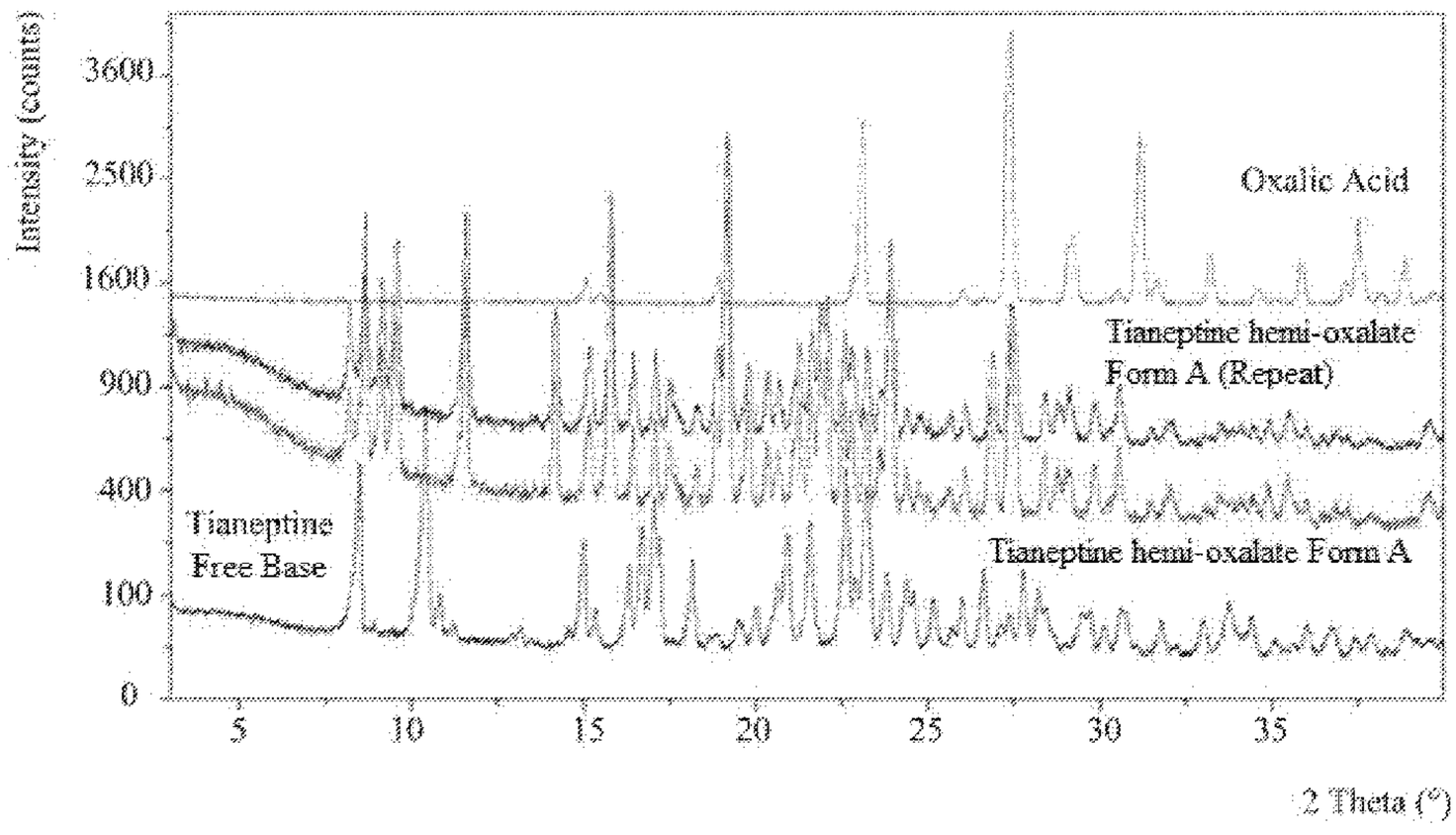
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

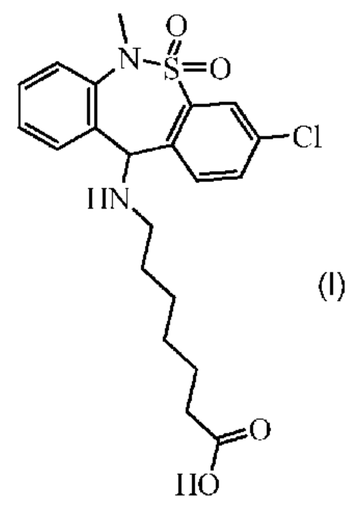
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: TIANEPTINE OXALATE SALTS AND POLYMORPHS

Figure 1





(I)

(57) Abstract: Disclosed herein is an oxalate salt/co-crystal (tianeptine oxalate) of (RS)-7-(3-chloro-6- methyl-6,11-dihydrodibenzo[c, f] [1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide (tianeptine) as shown in Formula (I).

WO 2018/122606 A1

TIANEPTINE OXALATE SALTS AND POLYMORPHS

FIELD OF THE INVENTION

[0001] The present disclosure is in the field of salts/co-crystals of tianeptine, including polymorphic forms of tianeptine oxalate, methods of making the salts and polymorphic forms, and pharmaceutical compositions comprising them are also described.

RELATED APPLICATIONS

[0002] This application claims the benefit of and priority from United States Provisional Application 62/439,533, filed December 28, 2016, the contents and disclosures of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

[0003] Tianeptine, or 7-[(3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][2,1]benzothiazepin-11-yl)amino]heptanoic acid, is an antidepressant with cognitive restorative effects. Investigators have reported that it can be used to treat post-traumatic stress disorder (PTSD) (Onder E. et al., (2005), *European Psychiatry* 21:174-179).

[0004] Although tianeptine shares structural similarities to classic tricyclic antidepressants, its pharmacological behavior is unique. More commonly known by the commercial names Stablon®, Coaxil, Tatinol, Tianeurax, and Salymbra, tianeptine is currently available throughout Europe, Asia, and Latin America for the treatment of depression. Tianeptine modulates the glutamatergic system and reverses the inhibitory neuroplasticity observed during periods of stress and steroid use. In modulating the glutamatergic system, tianeptine normalizes glutamate levels in the hippocampus, amygdala, and prefrontal cortex. Through genomic and non-genomic mechanisms, glutamate modulation restores plasticity, relieves inhibition of long-term potentiation, and reverses structural changes induced by chronic exposure to corticosteroids.

[0005] Tianeptine's anxiolytic properties and its reported ability to modulate the neuroendocrine stress response suggest that it can be used to treat PTSD. In fact, several studies have shown tianeptine to be an effective therapy for patients with PTSD because it is reported to improve many of the condition's characteristic symptoms (Crocq L & Goujon C: The Anxio-Depressive component of the psychotraumatic syndrome and its treatment by tianeptine. *Psychol Med*, 1994; 26 (2): 192-214; Rumyantseva GM & Stepanov AL: Post-traumatic stress disorder in different types of stress (clinical features and treatment). *Neurosci Behav Physiol*, 2008; 38:55-61; and Frančišković, Tanja, *et al.* "Tianeptine in the combined treatment of combat related posttraumatic stress disorder." *Psychiatria Danubina* 23(3) (2011): 257-263).

[0006] In addition to tianeptine's neuro-protective actions, including its ability to reverse the structural changes and inhibition of long term potentiation (LTP) caused by steroid exposure, it is reported to be potentially useful for treating neurocognitive dysfunction and similar side effects in patients treated with corticosteroids. Tianeptine's ability to restore cognitive functionality has also been observed in some animal models.

[0007] Due to their anti-inflammatory properties, corticosteroids are used in the treatment of many diseases and conditions including asthma, systematic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, nephritic syndrome, cancer, organ transplantation, autoimmune hepatitis, hypersensitivity reactions, cardiogenic and septic shock, glucocorticoid deficiency diseases (Addison's disease and panhypopituitarism), and multiple sclerosis. When the body experiences stress, the adrenal glands release corticosteroids, such as cortisol. Synthetic corticosteroids work by mimicking steroid hormones naturally produced by the adrenal glands. Upon release into the body's circulatory system, these hormones help to regulate inflammation as well as the body's immune response. Common synthetic corticosteroids include prednisone, cortisone, hydrocortisone, and methylprednisone. Supplementing the body's normal hormone levels with synthetic corticosteroids induces a genomic cascade that reduces inflammation and suppresses the immune response. This genomic cascade is initiated by the binding of steroids to intracellular glucocorticoid receptors (GRs) (Datson, NA et al.

Identification of corticosteroid-responsive genes in rat hippocampus using serial analysis of gene expression. *European Journal of Neuroscience*. 2001; 14(4): 675-689).

[0008] Despite their widespread use and therapeutic benefit, synthetic corticosteroids often cause numerous adverse psychological, metabolic, and somatic side effects (Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clinic Proceedings*. 2006; 81(10)). Examples of such somatic side effects are displayed in Table 1. Psychological side effects include mood and anxiety disorders, behavioral disturbance, cognitive impairment, and psychosis.

Table 1. Somatic Side Effects of Corticosteroid Use

Cardiovascular	Hypertension Accelerated atherosclerosis
Dermatologic	Acne Alopecia Hirsutism Striae Skin atrophy Purpura
Endocrine/Metabolic	Obesity Diabetes Mellitus Adrenal-pituitary axis suppression Hyperlipidemia Fluid and sodium retention Loss of potassium, calcium, and nitrogen Delayed growth
Neurologic	Pseudotumor cerebri
Gastrointestinal	Peptic ulcer disease Pancreatitis Fatty liver
Hematologic	Leukocytosis Neutrophilia Lymphophenia
Infectious	Oral candidiasis Increased risk of systemic infection
Musculoskeletal	Myopathy Osteoporosis Avascular necrosis
Ophthalmologic	Cataracts Glaucoma

[0009] Cognitive impairment, anxiety and mood disorders are among the most common psychological side effects of corticosteroid use. Especially for patients who require long-term steroid treatment, these effects result in a diminished quality of life. For example, 33% of individuals taking corticosteroids (about 13 million) are reported to exhibit deficits in working or short-term memory, declarative memory, attention span and concentration (academic & occupational performance), and executive functioning (Stoudemire A, Anfinson T, Edwards J. Corticosteroid-induced delirium and dependency. *Gen Hosp Psychiatry*. 1984; 141: 369-372). In extreme cases, steroids can even induce delirium, dementia (persistent memory impairment), and mania (Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. *Am J Psychiatry*. 1984; 141:369-372).

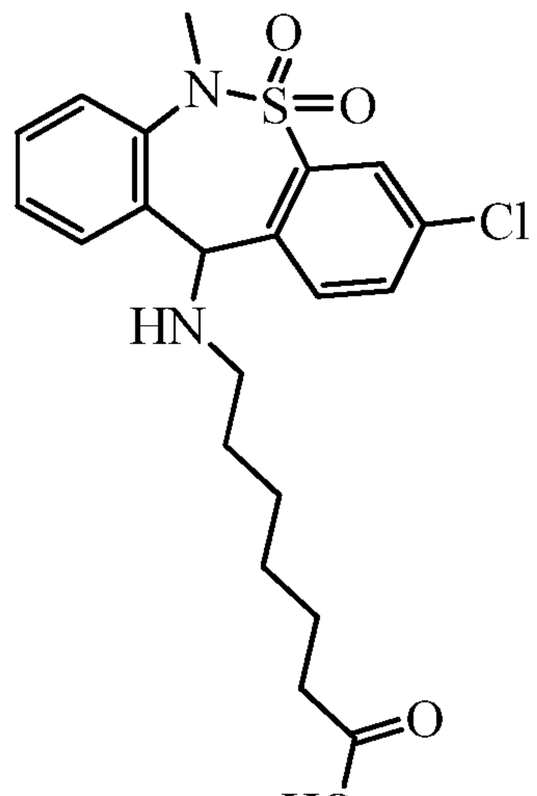
[0010] Currently, there is no FDA approved drug designated for the treatment of the cognitive impairment and similar psychiatric disorders, such as anxiety and mood disorders, associated with corticosteroid use. Tricyclic antidepressants do not appear to be useful therapeutic agents to modulate the psychiatric side effects induced by steroids, and may actually exacerbate these symptoms (Lewis DA, Smith RE. Steroid-induced Psychiatric Syndromes: A Report of 14 Cases and a review of the Literature. *Journal of Affective Disorders*. 1983; 5: 319-332). In addition, there are no alternatives to corticosteroids for the treatment of inflammatory disorders – corticosteroids must be used.

[0011] The disclosure herein relates to more stable chemical formulations, crystalline salts and polymorphs thereof of tianeptine for use in the treatment of neurocognitive dysfunction and related psychiatric disorders induced by corticosteroid treatment. These disorders include trauma- and stressor-related disorders including PTSD and acute stress disorder; depressive disorders including major depressive disorder, persistent depressive disorder, bipolar depression, and premenstrual dysphoric disorder; neurodegenerative diseases such as Alzheimer's disease and multi-infarct dementia; and neurodevelopmental disorders including attention-deficit\hyperactivity disorder. The

present disclosure can also be used in the treatment of asthma and chronic obstructive pulmonary disorder.

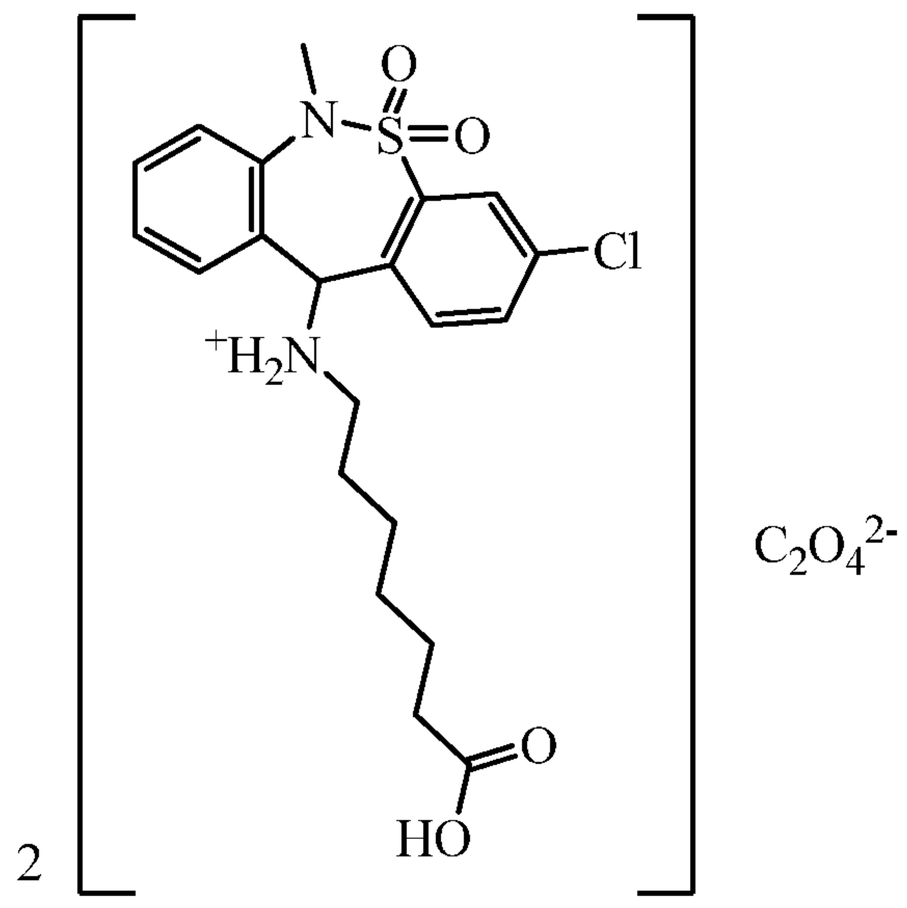
SUMMARY OF THE INVENTION

[0012] In some aspects, the disclosure herein comprises an oxalate salt/co-crystal (tianeptine oxalate) of (RS)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide (tianeptine) as shown in Formula I, including crystalline and polymorph forms:



Formula I.

[0013] The tianeptine hemi-oxalate salt is shown as Formula (II):



Formula II.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1: Overlayed XRPD patterns of tianeptine hemi-oxalate Form A, tianeptine free base and oxalic acid.

[0015] Figure 2: XRPD pattern of tianeptine hemi-oxalate Form A.

[0016] Figure 3: DSC profile of tianeptine hemi-oxalate Form A.

[0017] Figure 4: TGA profile of tianeptine hemi-oxalate Form A.

[0018] Figure 5: FTIR spectrum of tianeptine hemi-oxalate Form A.

[0019] Figure 6: 1H NMR spectrum (in DMSO-d_6) of tianeptine hemi-oxalate Form A.

[0020] Figure 7: Ortep drawing of the asymmetric unit with elipsoids of tianeptine hemi-oxalate (dianion).

[0021] Figure 8**:** Hydrogen bonds between the oxalate (central) and the four molecules of tianeptine.

[0022] Figure 9: XRPD comparison between tianeptine free base, tianeptine hemi-oxalate Form A, and tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A.

[0023] Figure 10: XRPD pattern of tianeptine mono-oxalate Form A.

[0024] Figure 11: FT-IR spectrum for tianeptine mono-oxalate Form A.

[0025] Figure 12: DSC profile of tianeptine mono-oxalate Form A.

[0026] Figure 13: TGA profile of tianeptine mono-oxalate Form A.

[0027] Figure 14: XRPD pattern of tianeptine mono-oxalate Form B.

[0028] Figure 15: FT-IR spectrum of tianeptine mono-oxalate Form B.

[0029] Figure 16: DSC profile of tianeptine mono-oxalate Form B.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0030] The present disclosure relates to salt/co-crystal forms of tianeptine oxalate, more particularly tianeptine hemi-oxalate and/or tianeptine mono-oxalate. The properties of the salts/co-crystals of tianeptine are improved relative to one or more known forms of tianeptine, such as tianeptine free base or tianeptine sodium (the currently available form of tianeptine). The salts/co-crystals can take several forms including, but not limited to, hydrates and solvates as well as various stoichiometric ratios of tianeptine to oxalic acid. The disclosure also includes other forms of tianeptine oxalate including, but not limited to, polymorphs and amorphous forms. The disclosure also provides pharmaceutical compositions comprising the salts/co-crystals of tianeptine oxalate, methods of making those salts/co-crystals, and related methods of treatment.

[0031] One embodiment of this disclosure is an oxalate salt/co-crystal (tianeptine oxalate).

[0032] In some embodiments, the tianeptine oxalate is crystalline.

[0033] In some embodiments, the salt/co-crystal is crystalline tianeptine hemi-oxalate Form A, tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or mixtures thereof.

[0034] In some embodiments, the salt/co-crystal is anhydrous crystalline tianeptine hemi-oxalate Form A, tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or combinations thereof.

[0035] A pharmaceutical composition comprising the salt/co-crystal of tianeptine oxalate and a pharmaceutically acceptable carrier, diluent or excipient.

[0036] In some embodiments, the salt/co-crystal of the pharmaceutical composition is anhydrous crystalline tianeptine hemi-oxalate Form A, mono-oxalate Form A, or a combination thereof.

[0037] In some embodiments, the salt/co-crystal of the pharmaceutical composition is tianeptine hemi-oxalate Form A.

[0038] In some embodiments, the anhydrous crystalline tianeptine hemi-oxalate Form A exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 8.2, 8.6, 9.1, and 9.5 degrees 2θ.

[0039] In some embodiments, the anhydrous crystalline tianeptine hemi-oxalate Form A exhibits an XRPD pattern comprising at least one peak at about 8.2, 8.6, 9.1, and 9.5 degrees 2θ with an associated tolerance of 0.3 degrees 2θ.

[0040] In some embodiments, the anhydrous crystalline tianeptine hemi-oxalate Form A exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 4.5, 8.2, 8.6, 9.1, 9.5, 11.5, 14.2, 15.2, 15.8, 16.4, 19.2, 22.1, 23.9, 26.9, and 27.4 degrees 2θ.

[0041] In some embodiments, the anhydrous tianeptine hemi-oxalate crystalline Form A exhibits an XRPD pattern substantially the same as Figure 2.

[0042] In some embodiments, the anhydrous crystalline tianeptine hemi-oxalate Form A is characterized by at least one of a) an XRPD pattern exhibiting at least four of the peaks shown in Figure 2; b) an FT-IR spectrum substantially the same as Figure 5; and c) an NMR spectrum substantially the same as Figure 6.

[0043] In some embodiments, the crystalline form is a tianeptine mono-oxalate Form A.

[0044] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form A exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 10.2 and 10.5 degrees 2θ.

[0045] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form A exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 10.2 and 10.5 degrees 2θ with an associated tolerance of 0.3 degrees 2θ.

[0046] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form A exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 7.5, 8.3, 10.2, 10.5, 11.9, 14.7, 16.2, 16.3, 17.9, 18.7, 21.0, 21.7, and 22.1 degrees 2θ.

[0047] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form A exhibits an XRPD pattern substantially the same as Figure 10.

[0048] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form A is characterized by at least one of a) an XRPD pattern exhibiting at least four of the peaks shown in Figure 10; and b) an FT-IR spectrum substantially the same as Figure 11.

[0049] In some embodiments, the crystalline form is a tianeptine mono-oxalate Form B.

[0050] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form B exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 10.4 and 10.8 degrees 2θ.

[0051] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form B exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 10.4 and 10.8 degrees 2θ with an associated tolerance of 0.3 degrees 2θ.

[0052] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form B exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 7.4, 7.8, 10.4, 10.8, 13.7, 14.8, 15.6, 16, 17.5, 19.9, 21.0, 20.2, 20.4, 20.9, 21.3, 21.6 and 21.9 degrees 2θ.

[0053] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form B exhibits an XRPD pattern substantially the same as Figure 14.

[0054] In some embodiments, the anhydrous crystalline tianeptine mono-oxalate Form B is characterized by at least one of a) an XRPD pattern exhibiting at least four of the peaks shown in Figure 14; and b) an FT-IR spectrum substantially the same as Figure 15.

[0055] In some embodiments, the pharmaceutical composition is in a solid form, a liquid form, a suspension form, a sustained release form, a delayed release form, or an extended release form.

[0056] In some embodiments, the anhydrous tianeptine oxalate crystalline form comprises a mixture of tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A.

[0057] In some embodiments, the anhydrous tianeptine oxalate crystalline form comprises a mixture of tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A, wherein the anhydrous tianeptine oxalate crystalline form exhibits an XRPD pattern comprising at least one peak selected from the group consisting of about 10.2 and 10.5 degrees 2θ.

[0058] In some embodiments, the anhydrous tianeptine oxalate crystalline form comprises a mixture of tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A, wherein the anhydrous tianeptine oxalate crystalline form exhibits an XRPD pattern comprising at least one peak selected from the group consisting of about 10.2 and 10.5 degrees 2θ with an associated tolerance of 0.3 degrees 2θ.

[0059] In some embodiments, the anhydrous tianeptine oxalate crystalline form comprises a mixture of tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A, wherein the crystalline form exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 7.5, 8.3, 10.2, 10.5, 11.9, 14.7, 16.2, 16.3, 17.9, 18.7, 21.0, 21.7, and 22.1 degrees 2θ.

[0060] In some embodiments, the anhydrous tianeptine oxalate crystalline form comprises a mixture of tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A, wherein the crystalline form exhibits an XRPD pattern substantially the same as Figure 9.

[0061] The salt/co-crystal forms of the various embodiments of this disclosure provide improved stability, bioavailability, lower hygroscopicity, more consistent pK, and easier processing and manufacturing, including pharmaceutical compositions as compared to sodium tianeptine.

[0062] In one aspect, this disclosure also provides formulations of tianeptine oxalate salts to be developed as first generation therapy for the treatment of corticosteroid-induced psychological side effects.

[0063] The tianeptine oxalate in the salt/co-crystal forms of the various embodiments of the disclosure has a higher melting point than the formulation of tianeptine (Stablon®) currently used to treat depression, suggesting greater crystalline stability and thus improved product performance in tablet form. As such, tianeptine oxalate has easier tablet formation as compared to Stablon® and improved tolerability such as fewer adverse events and severe adverse events.

[0064] In some embodiments of this disclosure, the tianeptine hemi-oxalate (Form A) and/or mono-oxalate (Form A and/or Form B) salts can be incorporated into a pharmaceutical composition. In some embodiments, the composition is in any one the following forms: sustained release, controlled release, delayed release or extended

release. In some embodiments, the tianeptine hemi-oxalate and/or mono-oxalate mixtures can be incorporated into a hydrophilic matrix system with a polymer. The tianeptine hemi-oxalate and/or mono-oxalate mixtures are released by dissolution, diffusion and/or erosion from the hydrophilic matrix when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system.

[0065] In another embodiment, the tianeptine hemi-oxalate (Form A) and/or mono-oxalate (Form A and/or Form B) can be incorporated into a pharmaceutical composition comprising two or more layers of tianeptine hemi-oxalate and/or oxalate such that one layer is substantially released prior to the substantial release of another layer *in vivo*. In another embodiment, the hemi-oxalate and/or oxalate salt of tianeptine can be incorporated into a pharmaceutical composition comprising pellets, wherein the pellets have varying extents or compositions of coating so as to enable release of tianeptine over a substantially longer period of time than that of the currently available tianeptine (e.g., STABLON®, Coaxil, or Tatinol).

[0066] In another embodiment, the hemi-oxalate (Form A) and/or mono-oxalate (Form A and/or Form B) salt of tianeptine can be incorporated into an osmotically active pharmaceutical composition suitable for oral administration. Osmotically active pharmaceutical compositions, osmotic pumps, osmotic drug delivery, and other osmotic technology suitable for oral administration can include, but are not limited to, OROS® Push-Pull and OROS® Tri-layer pharmaceutical compositions. In another embodiment, the tianeptine hemi-oxalate (Form A) and/or mono-oxalate (Form A and/or Form B) salt of tianeptine can be incorporated into an OROS® drug delivery system. Such controlled release pharmaceutical compositions comprising the oxalate salt of tianeptine, such as an osmotically active pharmaceutical composition suitable for oral administration, may lead to a longer lasting therapeutic effect than that of tianeptine sodium salt in the currently marketed form.

[0067] In some embodiments, the compositions of this disclosure may be in solid dosage forms such as capsules, tablets, dragrees, pills, lozenges, powders and granule.

Where appropriate, they may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled releases of one or more active ingredient such as sustained or prolonged release according to methods well known in the art. In certain embodiments, the composition is in form of a slow, controlled, or extended release. The term "extended release" is widely recognized in the art of pharmaceutical sciences and is used herein to refer to a controlled release of an active compound or agent from a dosage form to an environment over (throughout or during) an extended period of time, e.g. greater than or equal to one hour. An extended release dosage form will release drug at substantially constant rate over an extended period of time or a substantially constant amount of drug will be released incrementally over an extended period of time. The term "extended release" used herein includes the terms "controlled release", "prolonged release", "sustained release", or "slow release", as these terms are used in the pharmaceutical sciences. The composition may also be in liquid dosage forms including solutions, emulsions, suspensions, syrups, and elixirs. The composition may be formulated for once daily administration.

INSTRUMENTAL TECHNIQUES

Instrumental Techniques

[0068] Identification of the crystalline forms obtained by the present invention can be made by methods known in the art, including but not limited to X-Ray powder diffraction (XRPD), Fourier Transform Infrared (FT-IR) spectra, Differential Scanning calorimetry (DSC), Thermogravimetric Analysis (TGA), and Nuclear Magnetic Resonance (NMR). Furthermore, it should be understood that operator, instrument and other related changes may result in some margin of error with respect to analytical characterization of the salts/co-crystals.

Differential Scanning Calorimetry:

[0069] The analysis was carried out on the untreated sample using a DSC Mettler Toledo DSC1. The sample was weighed in an aluminum pan hermetically sealed with an aluminum cover. The analysis was performed by heating the sample from 25°C to 350°C at 10K/min.

Table 2. Technical Specification

Temperature range	-170 °C … 600 °C
Heating rates	0.001 K/min … 100 K/min
Cooling rate	0.001 K/min … 100 K/min (depending on temperature)
Sensor	Heat flux system
Measurement range	0 mW …± 600 mW
Temperature accuracy	0.1 K
Enthalpy accuracy	Generally <1%
Cooling options	Forced air (down to RT), LN2 (down to -170°C)
Purge gas rate	60 mL/min
Intracooler for the extended rate	-40°C … 600°C

Thermogravimetric Analysis:

[0070] The TG analysis was carried out on an untreated sample using the Mettler Toledo TGA/DSC1. The sample was weighed in an aluminum pan hermetically sealed with an aluminum pierced cover. The analysis was performed by heating the sample from 25°C to 450°C at 10K/min.

Table 3. Temperature Data

Temperature range	RT … 1100 °C
Temperature accuracy	± 1 K
Temperature precision	± 0.4 K
Heating rate	0.02 … 250 K/min
Cooling time	20 min (1100 °C … 100 °C)
Sample volume	≤100 µL

Table 4. Special modes

Automation	34 sample positions
TGA-FTIR	Coupled with Thermo Nicolet iS10 spectrometer
Balance data	XP5
Measurement range	≤5 g
Resolution	1.0 µg
Weighing accuracy	0.005%
Weighing precision	0.0025%

Internal ring weights	2
Blank curve reproducibility	Better than ± 10 µg over the whole temperature range

X-Ray Powder Diffraction (XRPD):

[0071] X-ray powder diffraction patterns were obtained using an X'Pert PRO PANalytical X-ray Diffractometer.

[0072] The X'Pert PRO PANalytical X-ray Diffractometer was equipped with a copper source (Cu/K_α1.5406 Å). Diffractogram was acquired using control software (X'Pert Data Collector vs. 2.2d) under ambient conditions at a power setting of 40 kV at 40 mA in reflection mode, while spinning over 360 degrees at 1 degree/second.

Table 5. (X-Ray Powder Diffraction (XRPD): Measurement Details)

Measurement type:	Single scan
Sample mode:	Reflection
Scan	
Scan axis:	Gonio
Scan range (°):	3,0010 – 39,9997
Step size (°):	0,0167
Counting time (s):	12,700
No. of points:	2214
Scan mode:	Continuous
Used wavelength	
Intended wavelength type:	Kα1
Kα1 (A):	1,540598
Kα2 (A):	1,544426
Kα2/Kα1 intensity ratio:	0,50
Kα (A):	1,541874
Kβ (A):	1,392250
Incident beam path	
Radius (mm):	240,0

Table 6. (X-Ray Powder Diffraction (XRPD): X-Ray Tube)

Name:	PW3373/00 Cu LFF DK184511
Anode material:	Cu
Voltage (kV):	40
Current (mA):	40
Focus	
Focus type:	Line
Length (mm):	12.0
width (mm):	0.4
Take-off angle (°):	6.0
Soller slit	
Name:	Soller 0.04 rad.
Opening (rad.):	0.04
Mask	
Name:	Inc. Mask Fixed 15 mm (MPD/MRD)
Width (mm):	11.60
Anti-scatter slit	
Name:	Slit Fixed 1/2°
Type:	Fixed
Height (mm):	0.76
Divergence slit	
Name:	Slit Fixed 1/4°
Type:	Fixed
Height (mm):	0.76
Sample movement	
Movement type:	Spinning
Rotation time (s):	1.0
Diffracted beam path	
Radius (mm):	240.0
Anti-scatter slit	
Name:	Anti-Scatter Slit 5.0 mm
Type:	Fixed

Height (mm):	5.00
Soller slit	
Name:	Soller 0.04 rad.
Opening (rad.):	0.04
Filter	
Name:	Nickel
Thickness (mm):	0.020
Material:	Ni

Table 7. (X-Ray Powder Diffraction (XRPD): Detector)

Name:	X'Celerator
Type:	RTMS detector
PHD - Lower level (%):	39,5
PHD - Upper level (%):	80,0
Mode:	Scanning
Active length (°):	2,122

***Fourier Transform Infrared Spectroscopy (FT-IR*):**

[0073] The analysis was carried out on an untreated sample using a Thermo Nicolet iS50 - ATR module Spectrometer equipped with a Smart Performer Diamond, DTGS KBr Detector, IR Source, and KBr Beam splitter. The sample was measured using the parameters described the Table 8 below.

Table 8. Experimental Conditions

Resolution	4000-650 cm-1
Number of sample scans	32
Number of background scans	32
Sample gain	8
Optical Velocity	0.6329
Aperture	100,00

Nuclear Magnetic Resonance (NMR):

[0074] The 1H NMR spectra were acquired at ambient temperature on a Gemini Varian 400 MHz spectrometer. Samples were prepared for NMR spectroscopy as ~5-50 mg solutions in DMSO-d6. For each sample 16 transients with a delay of t1=1 sec were collected at 25 °C.

Crystal Structure Data:

[0075] All crystal data were collected on an Oxford Xcalibur S instrument using Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator at room temperature. SHELX97 was used for structure solution and refinement and was based on F2. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms bound to carbon and nitrogen atoms were added in calculated positions. Hydroxyl hydrogen atoms were located using a Fourier map and their position refined. The program mercury was used for figure and calculation of X-ray powder patterns on the basis of single-crystal data.

DEFINITIONS

[0076] For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." As used herein, the meaning of the term "about" depends upon the context in which it is used. When used with respect to the position of a peak on an X-ray powder diffraction (XRPD) pattern, the term "about" includes peaks within an associated tolerance of ±0.3 degrees 2θ. For example, as used herein, an XRPD peak at "about 10.0 degrees 2θ" means that the stated peak occurs from 9.7 to 10.3 degrees 2θ. When used with respect to the position of a peak on a solid state 13C NMR spectrum, the term "about" includes peaks within ±0.2 ppm of the stated position. For example, as used herein, a 13C NMR spectrum peak at "about 100.0 ppm" means that the stated peak occurs from 99.8 to 100.2 ppm. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained.

[0077] As used herein, the term "substantially" in reference to an XRPD pattern refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance of ±0.3 degrees 2θ within the referenced peaks. In reference to an NMR pattern, "substantially" refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance of ±0.2 ppm within the referenced peaks. In reference to an FT-IR pattern, "substantially" refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance of ± 0.5 cm^{-1} within the referenced peaks.

[0078] As used herein, the term "co-crystal" refers to a molecular adduct of two molecules, each of which is solid at room temperature. A tianeptine oxalate co-crystal is a molecular adduct of tianeptine and any one of oxalate, hemi-oxalate, and mono-oxalate. The two molecules of the adduct form hydrogen bonds without transferring hydrogen between the molecules.

[0079] As used in this specification and the appended claims, the singular forms "a," "an," and "the," include plural references unless expressly and unequivocally limited to one referent.

[0080] As used herein, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

[0081] As used herein, the term "comprising" means including elements or steps that are identified following that term, but any such elements or steps are not exhaustive, and an embodiment can include other elements or steps.

[0082] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

Example 1

Tianeptine Hemi-oxalate Form A

[0083] 100-1000 mg of (RS)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide-the starting material (SM) and 20-200 mg of oxalic acid (1 eq.) were mixed in acetone (2-20 mL) and the solution was heated at 40-60 °C until total dissolution occurred. The clear solution was cooled at room temperature and stirred for 12-24 hours. The white precipitate was recovered under vacuum, washed with acetone and dried at 40-60 °C for 12-24 hours.

Table 9. Characterization details of Tianeptine Hemi-Oxalate Form A

Techniques/experiment	Results for Tianeptine Hemi Oxalate Form A
Synthesis	Tianeptine hemi oxalate Form A was prepared by precipitation from an acetone solution of tianeptine and oxalic acid
XRPD	The evidenced crystalline form was labeled as Form A
FT-IR	The infrared spectrum confirmed the formation of a new species
DSC	The DSC profile showed an endothermic peak at approximately 205°C (Onset 204.43 °C).
TGA	The TGA profile was typical of an anhydrous compound decomposing above 200 °C. EGA showed the evolution of CO_2 confirming the presence of the coformer
1H-NMR	1H-NMR confirmed the structural integrity of the tianeptine whereas the coformer was not visible. The protons of the molecule underwent slight shifts in their resonance frequencies

DSC/TGA

[0084] The DSC profile of tianeptine hemi-oxalate Form A as illustrated in Figure 3 was characterized by an endothermic event which took place just before sample decomposition. The peak at 205°C (Onset 204.43°C) was due to the sample melting and the broad shoulder was associated with decomposition.

[0085] The TGA profile of tianeptine hemi-oxalate Form A as illustrated in Figure 4 is typical of an anhydrous compound. Sample decomposition was characterized by the first weight loss of 8.13% w/w, which corresponded to 0.5 equivalents of oxalic acid. A stoichiometry of 1: 0.5 between tianeptine: oxalic acid was suggested. The oxalate showed a very high melting point above the 200 °C, when the melting and decomposition occurred at the same time.

XRPD

[0086] Figures 1 and 2 illustrate the XRPD pattern of the tianeptine hemi-oxalate salt.

Table 10. XRPD peaks list of Tianeptine hemi-oxalate Form A

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4,5010	34,97	0,9368	19,63245	1,56
8,2252	607,21	0,0669	10,74980	27,02
8,6666	1323,95	0,1004	10,20325	58,92
9,1460	799,69	0,0836	9,66947	35,59
9,5853	1166,90	0,1004	9,22727	51,93
11,5807	1467,88	0,1004	7,64149	65,33
14,1914	714,49	0,1004	6,24106	31,80
15,2018	454,39	0,0836	5,82843	20,22
15,7987	1647,80	0,1338	5,60952	73,33
16,4473	422,17	0,1004	5,38976	18,79
19,1657	2246,97	0,1506	4,63098	100,00
22,0891	773,13	0,0836	4,02427	34,41
23,9294	1253,33	0,1840	3,71878	55,78
26,8794	476,25	0,1673	3,31697	21,20
27,4168	751,73	0,1338	3,25317	33,46
28,3866	229,43	0,1171	3,14419	10,21
28,7606	152,29	0,1673	3,10416	6,78
29,1253	224,40	0,1171	3,06611	9,99
29,8763	174,82	0,1673	2,99072	7,78
30,6136	287,62	0,1171	2,92035	12,80
31,5515	44,50	0,1171	2,83565	1,98
32,1254	89,62	0,2676	2,78629	3,99

33,5303	64,44	0,1673	2,67270	2,87
34,4758	64,22	0,1338	2,60153	2,86
34,9300	96,39	0,1673	2,56873	4,29
35,4906	138,82	0,2007	2,52944	6,18
36,0079	82,53	0,1004	2,49428	3,67
36,4741	23,82	0,1004	2,46346	1,06
36,9223	65,21	0,1004	2,43458	2,90
37,8937	29,49	0,4684	2,37437	1,31
39,6005	74,60	0,2676	2,27588	3,32

[0087] The FT-IR spectrum and peaks of tianeptine hemi-oxalate Form A are illustrated in Figure 5 and Table 11. Comparison with the starting material showed many differences including the disappearance of the NH stretching at 3300 cm^{-1} and the appearance of the broad band at 1615 cm^{-1} from the C=O stretching ascribable to the presence of the oxalate.

Table 11. FT-IR Peak List of Tianeptine hemi-Oxalate Form A

Position (cm-1)	Intensity [%T]
432.49	62.178
466.63	50.071
488.10	54.917
519.00	60.449
539.59	38.578
570.25	27.820
584.10	25.441
602.02	50.697
633.03	83.567
670.00	56.310
692.71	61.686
724.21	47.215
765.61	28.950
814.36	71.754
847.32	51.291
876.39	70.707
900.03	63.088
911.81	64.771
958.77	81.157
1042.00	54.177
1055.28	61.901
1105.17	50.022
1138.76	50.102
1178.74	39.915
1235.36	39.678
1344.85	43.888

1434.82	66.912
1493.92	62.230
1614.97	60.669
1679.91	82.130
2932.88	86.038
3210.13	92.735

NMR

[0088] 1H-NMR of tianeptine hemi-oxalate Form A (see Figure 6) showed that the signals of the protons near the amine moiety were shifted downfield compared to the starting material. This suggests a possible interaction between the basic nitrogen and a carboxylic moiety of the coformer. Neither the presence of the coformer nor the stoichiometry of the sample could be confirmed by 1H-NMR analysis.

[0089] 1H-NMR (400 MHz, dmso-d6) δ (ppm): 1.10-1.32 (m, 4H), 1.38-1.54 (m, 4H), 2.16 (t, J = 7.5 Hz, 2H), 2.40-2.58 (br band, 2H + DMSO-d6), 3.37 (s, 3H), 5.34 (s, 1H), 7.33-7.60 (m, 4H), 7.76 (br s, 2H), 7.82 (br s, 1H).

[0090] Tianeptine hemi-oxalate Form A crystallizes as triclinic P-1 where a =9.5477(7)Å, b =11.4514(10)Å, c= 11.8918(12)Å, α= 113.071(9), β= 94.351(7) ° and γ= 100.164(7)°. The asymmetric unit is made of one protonated tianeptine molecule and half molecule of oxalate (see Figure 7). The stoichiometry of the salt is 2:1 tianeptine to oxalate meaning the oxalate is a dianion.

[0091] The oxalate dianion forms hydrogen bonds with four different tianeptine molecules (see Table 12 and Figure 8). The tianeptine carboxylic group interacts with the carboxylate group, while the amino group forms a bifurcated hydrogen bond with the two oxygen atoms of the oxalate as shown in Figure 8.

Table 12. Hydrogen bond distances in tianeptine hemi-oxalate

Donor-H···Acceptor	**Distance (Å)**
Intra N(1) --H(1B) ..O(1)	2.762(3)
O(3) --H(300) ..O(7)	2.551(4)
N(1) --H(1A) ..O(7)	2.788(3)
N(1) --H(1A) ..O(6)	2.735(3)

Table 13. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å2x 10^3) for tianeptine hemi-oxalate Form A

	x	y	Z	U(eq)
C(14)	1205(3)	6111(3)	3786(3)	41(1)
C(1)	5009(3)	7193(3)	4985(3)	34(1)
C(2)	5571(4)	7638(3)	6220(3)	45(1)
C(3)	5203(4)	8732(3)	7060(3)	53(1)
C(4)	4321(4)	9369(3)	6677(3)	51(1)
C(5)	3757(3)	8902(3)	5434(3)	42(1)
C(6)	4083(3)	7804(3)	4558(3)	33(1)
C(7)	3349(3)	7316(3)	3232(3)	34(1)
C(8)	4245(3)	7116(3)	2186(3)	34(1)
C(9)	3644(4)	7303(3)	1189(3)	50(1)
C(10)	4305(4)	7160(4)	164(3)	62(1)
C(11)	5614(4)	6813(4)	118(3)	61(1)
C(12)	6235(4)	6615(3)	1078(3)	51(1)
C(13)	5578(3)	6764(3)	2120(3)	37(1)
C(15)	-56(3)	4935(3)	3249(3)	41(1)
C(16)	351(3)	3639(3)	2964(3)	45(1)
C(17)	-927(4)	2490(3)	2379(4)	60(1)
C(18)	-562(5)	1171(3)	2010(4)	73(1)
C(19)	125(5)	944(3)	3033(4)	68(1)
C(20)	477(4)	-368(3)	2746(4)	57(1)
C(21)	7782(4)	7559(4)	3692(4)	58(1)
N(1)	2204(2)	6082(2)	2887(2)	36(1)
N(2)	6413(3)	6588(2)	3078(2)	41(1)
O(1)	4442(2)	4906(2)	3091(2)	42(1)
O(2)	6693(3)	5568(2)	4545(2)	57(1)
O(3)	-238(3)	-1283(2)	1694(3)	70(1)
O(4)	1273(3)	-557(3)	3438(3)	92(1)
Cl(1)	5903(2)	9287(1)	8610(1)	98(1)
S(1)	5633(1)	5905(1)	3894(1)	40(1)
C(22)	-288(3)	5635(3)	208(3)	34(1)
O(6)	-1158(2)	5753(2)	-532(2)	52(1)
O(7)	207(2)	6468(2)	1306(2)	43(1)

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

5

Table 14. Bond lengths [Å] and angles [°] for tianeptine hemi-oxalate Form A

C(14)-N(1)	1.480(4)
C(14)-C(15)	1.519(4)
C(1)-C(2)	1.379(4)
C(1)-C(6)	1.399(4)
C(1)-S(1)	1.773(3)
C(2)-C(3)	1.386(5)
C(3)-C(4)	1.366(5)
C(3)-Cl(1)	1.730(3)
C(4)-C(5)	1.385(5)
C(5)-C(6)	1.386(4)
C(6)-C(7)	1.514(4)
C(7)-N(1)	1.514(3)
C(7)-C(8)	1.529(4)
C(8)-C(9)	1.386(4)
C(8)-C(13)	1.400(4)
C(9)-C(10)	1.381(5)
C(10)-C(11)	1.375(5)
C(11)-C(12)	1.361(5)
C(12)-C(13)	1.396(4)
C(13)-N(2)	1.440(4)
C(15)-C(16)	1.516(4)
C(16)-C(17)	1.514(4)
C(17)-C(18)	1.511(5)
C(18)-C(19)	1.471(5)
C(19)-C(20)	1.511(5)
C(20)-O(4)	1.184(4)
C(20)-O(3)	1.311(4)
C(21)-N(2)	1.478(4)
N(2)-S(1)	1.615(3)
O(1)-S(1)	1.426(2)
O(2)-S(1)	1.423(2)
C(22)-O(6)	1.227(3)
C(22)-O(7)	1.269(3)
C(22)-C(22)#1	1.555(6)
N(1)-C(14)-C(15)	111.5(2)
C(2)-C(1)-C(6)	122.4(3)
C(2)-C(1)-S(1)	118.2(2)
C(6)-C(1)-S(1)	119.1(2)
C(1)-C(2)-C(3)	118.3(3)
C(4)-C(3)-C(2)	121.1(3)
C(4)-C(3)-Cl(1)	120.6(3)
C(2)-C(3)-Cl(1)	118.3(3)
C(3)-C(4)-C(5)	119.8(3)
C(6)-C(5)-C(4)	121.4(3)
C(5)-C(6)-C(1)	117.1(3)
C(5)-C(6)-C(7)	117.8(3)
C(1)-C(6)-C(7)	125.0(2)

N(1)-C(7)-C(6)	110.6(2)
N(1)-C(7)-C(8)	108.5(2)
C(6)-C(7)-C(8)	120.3(2)
C(9)-C(8)-C(13)	117.0(3)
C(9)-C(8)-C(7)	115.1(3)
C(13)-C(8)-C(7)	127.8(3)
C(10)-C(9)-C(8)	122.8(3)
C(11)-C(10)-C(9)	119.2(4)
C(12)-C(11)-C(10)	119.7(4)
C(11)-C(12)-C(13)	121.5(3)
C(12)-C(13)-C(8)	119.8(3)
C(12)-C(13)-N(2)	114.5(3)
C(8)-C(13)-N(2)	125.7(3)
C(16)-C(15)-C(14)	114.7(2)
C(17)-C(16)-C(15)	112.9(3)
C(18)-C(17)-C(16)	114.9(3)
C(19)-C(18)-C(17)	115.1(3)
C(18)-C(19)-C(20)	118.3(3)
O(4)-C(20)-O(3)	123.6(3)
O(4)-C(20)-C(19)	122.8(3)
O(3)-C(20)-C(19)	113.5(3)
C(14)-N(1)-C(7)	116.0(2)
C(13)-N(2)-C(21)	116.4(3)
C(13)-N(2)-S(1)	120.6(2)
C(21)-N(2)-S(1)	116.4(2)
O(2)-S(1)-O(1)	118.86(14)
O(2)-S(1)-N(2)	108.81(14)
O(1)-S(1)-N(2)	107.18(13)
C(9)-C(8)-C(13)	117.0(3)
C(9)-C(8)-C(7)	115.1(3)
C(13)-C(8)-C(7)	127.8(3)
C(10)-C(9)-C(8)	122.8(3)
C(11)-C(10)-C(9)	119.2(4)
C(12)-C(11)-C(10)	119.7(4)
C(11)-C(12)-C(13)	121.5(3)
C(12)-C(13)-C(8)	119.8(3)
C(12)-C(13)-N(2)	114.5(3)
C(8)-C(13)-N(2)	125.7(3)
C(16)-C(15)-C(14)	114.7(2)
C(17)-C(16)-C(15)	112.9(3)
C(18)-C(17)-C(16)	114.9(3)
C(19)-C(18)-C(17)	115.1(3)
C(18)-C(19)-C(20)	118.3(3)
O(4)-C(20)-O(3)	123.6(3)
O(4)-C(20)-C(19)	122.8(3)
O(3)-C(20)-C(19)	113.5(3)
C(14)-N(1)-C(7)	116.0(2)
C(13)-N(2)-C(21)	116.4(3)
C(13)-N(2)-S(1)	120.6(2)

C(21)-N(2)-S(1)	116.4(2)
O(2)-S(1)-O(1)	118.86(14)
O(2)-S(1)-N(2)	108.81(14)
O(1)-S(1)-N(2)	107.18(13)
C(13)-N(2)-S(1)	120.6(2)
C(21)-N(2)-S(1)	116.4(2)
O(2)-S(1)-O(1)	118.86(14)
O(2)-S(1)-N(2)	108.81(14)
O(1)-S(1)-N(2)	107.18(13)
O(2)-S(1)-C(1)	108.21(14)
O(1)-S(1)-C(1)	110.17(13)
N(2)-S(1)-C(1)	102.35(14)
O(6)-C(22)-O(7)	125.7(3)
O(6)-C(22)-C(22)#1	118.6(3)
O(7)-C(22)-C(22)#1	115.6(3)

Solubility

[0092] The solubility of the tianeptine hemi-oxalate form A was compared with that of the tianeptine sodium salt at various pH using standard buffers as shown in Table 15 below.

Table 15. Solubility Comparison

Medium	**Prepared according to**	**Tianeptine Hemi-Oxalate Form A solubility (mg/ml)**	**Tianeptine Sodium solubility (mg/ml)**
pH 1.2	USP	0.702	4.645
pH 4.5 (Phosphate)	USP	0.313	2.101
pH 4.5 (Acetate)	PhEu	0.317	3.676
pH 6.8 (Phosphate)	USP	0.585	1.768
Water	20mg in 100ml	Soluble after 40 minutes of mixing with magnetic stirrer	Freely Soluble

Hygroscopicity

[0093] The hygroscopicity of the tianeptine hemi-oxalate Form A was compared that of the tianeptine sodium salt. Crystals of the tianeptine samples were observed in open air or in closed conditions (crimped glass vial) under varying temperature and relative humidity (RH) parameters as shown in Tables 16-17 below. Hygroscopicity was measured as the percentage (%) of water in the sample using the Karl Fisher (KF) method at day 1, 3, and 7. While tianeptine sodium is extremely hygroscopic (Table 17), the water content of the tianeptine hemi-oxalate salt was practically unchanged after 7 days, in open air or in a crimped glass vial (Table 16).

Table 16. Hygroscopicity of Tianeptine hemi-oxalate Form A

Tianeptine Hemi-Oxalate Form A	Time 0	Time 1day		Time 3days		Time 7days	
Storage Conditions		Open Air	Crimped glass vial	Open Air	Crimped glass vial	Open Air	Crimped glass vial
25°C, 60%RH	0.47%	0.35%	0.34%	0.28%	0.18%	0.22%	0.28%
30°C, 65%RH		0.28%	0.27%	0.18%	0.16%	0.30%	0.30%
40°C, 75%RH		0.06%	0.30%	0.30%	0.16%	0.17%	0.20%

Table 17. Hygroscopicity of Tianeptine Sodium

Tianeptine Sodium	Time 0	Time 1day		Time 3days		Time 7days	
Storage Conditions		Open Air	Crimped glass vial	Open Air	Crimped glass vial	Open Air	Crimped glass vial
25°C, 60%RH	3.09%	13.86%	2.94%	NP	2.42%	NP	2.56%
30°C, 65%RH		14.80%	2.63%	NP	2.65%	NP	2.77%
40°C, 75%RH		16.22%	2.84%	NP	2.73%	NP	2.53%

NP=Not performed due to visual decomposition of the extremely hygroscopic sample at day 1.

Example 2

Tianeptine hemi-oxalate and mono-oxalate Form A mixture

[0094] The above reaction was repeated at a smaller scale to confirm the formation of the new species. 10-100 g of tianeptine free base was dissolved in 200-2000 mL of acetone and the solution was heated at reflux. 2-20 g (1eq.) of oxalic acid were added to the clear solution and the resulting mixture was stirred at 40-60°C for 30-60 minutes. The coformer was instantly solubilized and a clear solution was observed. After a few minutes, the formation of a white precipitate was observed. The mixture was then cooled at room temperature and stirred for 12-24 hours. The white precipitate was recovered under vacuum, washed with acetone and dried at 40-60°C for 12-24 hours.

[0095] Replication of the reaction confirmed the presence of tianeptine mono-oxalate Form A in mixture with hemi-oxalate Form A. Such mixtures could also be obtained by mixing the two independently prepared species.

[0096] DSC analysis of the mixture showed two distinct endothermic peaks. The first endothermic peak at 176 °C (onset at 174.64°C) and the second endothermic peak was detected at 200 °C (onset 195.45 °C), which was imputable to the melting and decomposition of the tianeptine hemi-oxalate Form A. TG analysis confirmed that the sample was dried and that the decomposition occurred below 17°C in two distinct events where approximately 12% and 9 % of weight was lost.

[0097] Melting point analysis of the mixture highlighted that the first event observed during the DSC analysis was ascribable to the melting of the sample without its decomposition (as visible at 166, 178 and 188 °C). The second endothermic event started with the melting of the sample followed by decomposition.

Interconversion slurry tests

[0098] The mixture was subjected to slurry experiments to evaluate potential conversion between the two salts. 100 mg was suspended in 2 mL of a single solvent and left under magnetic stirring at approximately 200 rpm at room temperature for 3 and 7

days as well as at 50 °C for 3 days. Afterwards, the samples were checked by XRPD analyses and the resulting diffractograms were compared to the XRPD patterns of the starting material and that of tianeptine hemi-oxalate Form A. The results of the slurry experiments are shown in Table 18.

Table 18. Results of the slurry experiments

Solvent	Slurry-3days-RT	Slurry-7days-RT	Slurry-50°C-3days
Acetone	tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A	tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A	tianeptine hemi-oxalate Form A
Ethyl Acetate	tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A	tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A	tianeptine hemi-oxalate Form A + tianeptine mono-oxalate Form A

Stability of tianeptine hemi-oxalate salt

[0099] These analyses confirmed that tianeptine hemi-oxalate Form A is the most thermodynamically stable form due to its higher melting point and stability during slurry experiments. To assess the phase stability of the tianeptine hemi-oxalate Form A, several slurry experiments were performed in different solvents or solvent mixtures and different temperature conditions. No significant modifications in the XRPD pattern were observed after the tests. In addition, stability tests were carried out in different conditions of temperature (25-60°C) and relative humidity (0-75%C). In all the tested conditions, the crystal form did not Grinding and water kneading experiments were conducted as well and they did not induce a phase shift. Based on the slurry experiments and stability tests performed Tianeptine hemi-oxalate Form A can be considered the thermodynamic stable form.

[0100] When the reaction ratio between tianeptine and oxalic acid was 2:1, the formation of tianeptine hemi-oxalate Form A was preferred, whereas when the ratio was 1:1 in some low polar solvents, the formation of tianeptine mono-oxalate Form A was favored.

Example 3

Tianeptine mono-oxalate Form A

[0101] The following synthetic methodology was used to prepare tianeptine mono-oxalate Form A. 2-20 g of tianeptine was dissolved in 200-2000 mL of ethyl acetate under magnetic stirring at 40-60°C. After 15-30 minutes, the hot clear solution was cooled to room temperature and left under stirring for 90-180 minutes, but the solution remained clear. 1-10g of oxalic acid was dissolved in 20-200 mL of ethyl acetate at room temperature, obtaining a clear solution (concentration= 50 mg/mL). 8-80mL of the oxalic acid solution (1 eq.) was then added rapidly to the tianeptine solution under magnetic stirring at room temperature. A white powder instantly precipitated. After 60-90 minutes, the suspension was recovered under vacuum, washed with ethyl acetate, and dried under vacuum (10^{-2} atm) at room temperature overnight.

[0102] The XRPD diffraction pattern and its peak list for tianeptine mono-oxalate Form A are illustrated in Figure 10 and Table 19, respectively. The FT-IR spectrum for tianeptine mono-oxalate Form A is reported in Figure 11 and its peak list is reported in Table 20.

Table 19. XRPD Peaks List of Tianeptine mono-Oxalate Form A

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.7082	63.61	0.8029	15.48295	2.10
7.4941	709.24	0.1171	11.79669	23.46
8.2794	645.85	0.1171	10.67947	21.36
10.1224	3023.10	0.1338	8.73884	100.00
10.4738	2158.15	0.1338	8.44637	71.39
11.9311	1022.01	0.1171	7.41780	33.81
14.7375	1181.20	0.1171	6.01097	39.07
16.2068	732.25	0.0669	5.46918	24.22
16.3175	775.67	0.0836	5.43235	25.66
17.0803	441.14	0.1673	5.19140	14.59
17.9805	1507.42	0.1673	4.93348	49.86
18.1409	907.54	0.0836	4.89022	30.02
18.6654	1066.16	0.1506	4.75396	35.27
19.2422	130.86	0.1338	4.61275	4.33
19.8272	160.52	0.2007	4.47796	5.31
20.9993	2021.18	0.1840	4.23059	66.86
21.6871	986.74	0.1673	4.09795	32.64
22.0789	1127.40	0.2007	4.02611	37.29

22.7397	1599.50	0.0669	3.91058	52.91
22.9548	1145.78	0.1004	3.87441	37.90
23.3796	1431.11	0.1673	3.80498	47.34
23.9564	741.27	0.1428	3.71157	24.52
24.0542	767.99	0.0816	3.70589	25.40
24.9620	622.68	0.1224	3.56429	20.60
25.4332	493.19	0.0816	3.49931	16.31
25.8455	120.08	0.1224	3.44442	3.97
27.1812	272.70	0.1224	3.27811	9.02
28.2343	273.69	0.2856	3.15819	9.05
28.7192	564.65	0.1632	3.10596	18.68
29.8322	823.17	0.1428	2.99257	27.23
30.7901	374.48	0.1224	2.90161	12.39
31.8007	237.28	0.2856	2.81167	7.85
32.5020	239.28	0.1428	2.75258	7.91
33.7079	166.14	0.2040	2.65681	5.50
34.6256	49.87	0.2448	2.58847	1.65
35.1208	141.34	0.2448	2.55310	4.68
36.2371	158.16	0.2040	2.47697	5.23
36.5029	184.56	0.2448	2.45954	6.11
37.0868	179.15	0.3672	2.42215	5.93
38.2112	90.60	0.2448	2.35342	3.00
38.9995	95.43	0.4896	2.30765	3.16
39.7161	60.60	0.2448	2.26765	2.00

Table 20. FT-IR Peak List of Tianeptine mono-Oxalate Form A.

Position (cm-1)	**Intensity [%T]**
407	78.015
420	69.840
437	49.006
472	60.639
503	66.437
542	38.170
574	14.288
590	25.372
599	45.604
634	87.938
672	51.844
698	48.676
715	46.116
730	63.379
745	58.880
756	51.876
765	38.000
817	58.594
848	59.972
881	67.940
895	69.758

915	46.973
956	85.792
1012	82.832
1044	57.782
1058	61.391
1068	73.339
1103	53.620
1140	54.137
1162	39.190
1183	39.124
1206	58.980
1218	61.413
1241	35.677
1291	50.234
1319	66.721
1347	38.293
1393	55.381
1445	69.191
1459	74.454
1474	67.558
1500	73.813
1578	59.760
1623	44.368
1724	51.663
1763	57.945
2162	98.026
2324	93.872
2495	91.427
2633	89.069
2862	87.030
2932	84.185
3098	91.653
3177	86.700
3245	89.155

[0103] The DSC profile reported in Figure 12 showed a sharp endothermic peak at 175°C (onset 174.8°C), which was associated with the melting of the sample. It also showed an exothermic peak at 179°C associated to recrystallization of the sample. Two endothermic events were also observed at 196°C. These peaks were associated with the melting of tianeptine mono-oxalate Form A while the broad peak was due to the decomposition of the oxalic acid.

[0104] The TGA profile reported in Figure 13 only showed the degradation of the sample during the thermal events seen in the DSC profile. The weight loss caused by the decomposition of the oxalic acid in CO_2 WAS 16.4%

[0105] Tianeptine mono-oxalate Form A was anhydrous, slightly hygroscopic and started to convert into tianeptine hemi-oxalate Form A at 40 -60°C under high humidity (75%RH) and by water kneading. It appeared stable if it was milled without water and if it was stored in milder conditions (25°C and 60-75% RH) or at high temperatures (40-60°C) without humidity (RH≈0%).

[0106] No significant difference in the water solubility at room temperature was visually observed between the two forms (lower than 1 mg/mL).

Example 4

Tianeptine mono-oxalate Form B

[0107] To prepare tianeptine mono-oxalate Form B, 50mg of tianeptine free base was dissolved in 6.0 mL of nitromethane. 10 mg (1 equivalent) of oxalic acid was dissolved in 0.5 mL of nitromethane and the resulting solution was added to the solution of tianeptine. Immediately after the addition, the reaction mixture was cooled in an ice bath. After approximately 7 minutes, the white precipitate was recovered under vacuum and analyzed by XRPD.

[0108] The diffractogram and corresponding peak list of tianeptine mono-oxalate Form B are reported in Figure 14 and Table 21. The FT-IR spectrum of tianeptine mono-oxalate Form B is reported in Figure 15 and its peak list is reported in Table 22.

Table 21. XRPD Peaks List of Tianeptine mono-Oxalate Form B

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.9877	53.99	0.2007	14.76081	2.46
7.4484	644.86	0.1171	11.86894	29.42
7.8000	332.97	0.1171	11.33473	15.19
8.6132	2191.71	0.1506	10.26635	100.00
10.4137	1467.04	0.1338	8.49500	66.94
10.7756	561.19	0.1171	8.21054	25.61
12.0662	111.82	0.1338	7.33509	5.10
13.6920	257.13	0.0836	6.46751	11.73
14.8560	875.54	0.1840	5.96332	39.95
15.5731	811.65	0.1338	5.69028	37.03
16.0391	451.42	0.1506	5.52600	20.60
17.4715	795.13	0.1338	5.07603	36.28
17.8589	167.53	0.1338	4.96679	7.64
18.8422	163.02	0.1004	4.70975	7.44
19.2387	206.33	0.1338	4.61359	9.41
19.8786	562.24	0.1338	4.46648	25.65
20.2416	478.57	0.1004	4.38719	21.84
20.4483	579.19	0.1338	4.34331	26.43
20.9058	684.79	0.1171	4.24929	31.24
21.2650	622.71	0.1338	4.17831	28.41
21.6364	453.54	0.1338	4.10743	20.69
21.9569	437.70	0.1171	4.04820	19.97
22.7958	225.10	0.0669	3.90109	10.27
23.4708	1586.21	0.1506	3.79039	72.37
23.7824	397.64	0.1338	3.74144	18.14
24.3598	833.23	0.1506	3.65404	38.02
24.6971	1117.13	0.1506	3.60489	50.97
25.2005	227.05	0.1506	3.53402	10.36
25.7272	95.62	0.1338	3.46284	4.36
26.7623	64.66	0.1673	3.33121	2.95
27.3979	469.15	0.1171	3.25537	21.41
27.6142	248.09	0.1004	3.23036	11.32
29.0818	182.64	0.1004	3.07059	8.33
29.5176	62.93	0.1004	3.02624	2.87
30.1255	254.64	0.1506	2.96655	11.62
30.4403	205.52	0.1004	2.93658	9.38
30.8331	56.14	0.1338	2.90006	2.56
31.3986	69.24	0.1338	2.84911	3.16
31.7911	85.16	0.2007	2.81483	3.89
32.3064	438.17	0.1224	2.76880	19.99
32.4065	443.19	0.0816	2.76733	20.22
33.1884	54.59	0.1632	2.69721	2.49
33.8013	48.48	0.1632	2.64969	2.21
34.5438	170.40	0.1020	2.59441	7.77
35.4188	36.28	0.2448	2.53230	1.66
35.8785	69.62	0.1224	2.50091	3.18

36.2912	126.50	0.2040	2.47341	5.77
37.2195	37.44	0.2448	2.41382	1.71
38.2239	25.23	0.2856	2.35267	1.15
39.0687	83.00	0.2040	2.30372	3.79

Table 22. FT-IR Peak List of Tianeptine mono-Oxalate Form B

Position (cm-1)	Intensity [%T]
417	80.583
433	60.709
470	61.112
490	73.589
506	74.658
542	44.891
573	33.138
588	34.548
598	45.975
636	88.682
672	64.770
697	62.702
718	53.966
726	58.476
743	69.288
754	66.477
767	56.363
806	74.846
817	74.210
842	71.115
858	71.329
892	75.547
913	60.377
1009	87.441
1043	64.997
1053	74.675
1066	76.779
1107	63.129
1140	60.337
1181	44.309
1217	50.155
1240	43.325
1289	69.256
1355	58.928
1407	72.611
1445	80.501
1474	80.926
1495	79.647
1575	71.109
1618	58.270

1716	60.858
1755	70.768
2324	96.331
2859	88.179
2932	85.760
3178	90.209

[0109] The DSC profile (Figure 16) shows a sharp endothermic peak at 178°C (onset 177.3°C), which was associated with the sample melting. It also showed two endothermic events that took place at 197°C. These events were probably associated with the melting of tianeptine mono-oxalate while the broad peak was due to the decomposition of the oxalic acid.

[0110] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

[0111] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and devices within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods or devices, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

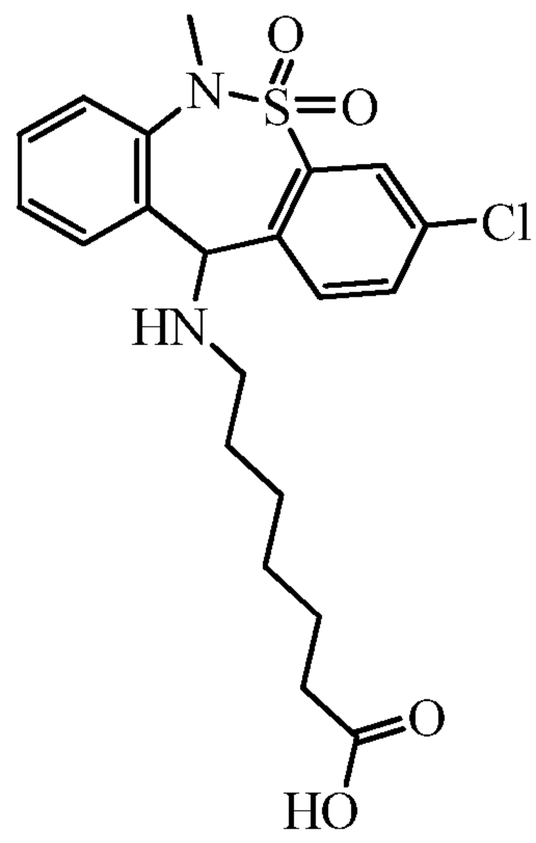
[0112] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual

publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict any definitions in this disclosure.

5

WHAT IS CLAIMED IS:

1. An oxalate salt/co-crystal (tianeptine oxalate) of (RS)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide (tianeptine) as shown in Formula I:



Formula I.

2. The salt/co-crystal of claim 1, wherein the tianeptine oxalate is crystalline.

3. The salt/co-crystal of claim 2, wherein the salt is a mixture of crystalline tianeptine hemi-oxalate Form A salt and tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or a combination thereof.

4. The salt/co-crystal of claim 2, wherein the salt is anhydrous crystalline tianeptine hemi-oxalate Form A, tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or a combination thereof.

5. A pharmaceutical composition comprising the salt/co-crystal of tianeptine oxalate with a pharmaceutically acceptable carrier, diluent or excipient.

6. The pharmaceutical composition of claim 5, wherein the salt/co-crystal is anhydrous crystalline tianeptine hemi-oxalate Form A, mono-oxalate Form A, or a combination thereof.

7. The anhydrous crystalline tianeptine hemi-oxalate Form A of claim 4, wherein the crystalline form exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 8.2, 8.6, 9.1, and 9.5 degrees 2θ.

8. The compound of claim 7, wherein the tianeptine hemi-oxalate crystalline Form A exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 4.5, 8.2, 8.6, 9.1, 9.5, 11.5, 14.2, 15.2, 15.8, 16.4, 19.2, 22.1, 23.9, 26.9, and 27.4 degrees 2θ.

9. The anhydrous tianeptine hemi-oxalate crystalline Form A of claim 4, wherein the crystalline Form A exhibits an XRPD pattern substantially the same as Figure 2.

10. The anhydrous crystalline tianeptine hemi-oxalate Form A of claim 4, characterized by at least one of:

(a) an XPRD pattern exhibiting at least four of the peaks shown in Figure 2;

(b) an FT-IR spectrum substantially the same as Figure 5; and

(c) an NMR spectrum substantially the same as Figure 6.

11. The anhydrous crystalline tianeptine mono-oxalate of claim 4, wherein the crystalline form exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak at about 10.2 and 10.5 degrees 2θ.

12. The compound of claim 11, wherein the crystalline form exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 7.5, 8.3, 10.2, 10.5, 11.9, 14.7, 16.2, 16.3, 17.9, 18.7, 21.0, 21.7, and 22.1 degrees 2θ.

13. The anhydrous crystalline tianeptine mono-oxalate Form A of claim 4, wherein the crystalline form exhibits an XRPD pattern substantially the same as Figure 10.

14. The anhydrous crystalline tianeptine mono-oxalate Form A of claim 4, characterized by an XPRD pattern exhibiting at least four of the peaks shown in Fig. 10.

15. The anhydrous tianeptine oxalate crystalline form of claim 4, wherein the crystalline form is tianeptine hemi-oxalate Form A and tianeptine mono-oxalate Form A.

16. The anhydrous tianeptine oxalate crystalline form of claim 15, wherein the crystalline form exhibits an XRPD pattern comprising at least one peak selected from the group consisting of about 10.2 and 10.5 degrees 2θ.

17. The compound of claim 16, wherein the crystalline form exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of about 7.5, 8.3, 10.2, 10.5, 11.9, 14.7, 16.2, 16.3, 17.9, 18.7, 21.0, 21.7, and 22.1 degrees 2θ.

18. The anhydrous crystalline tianeptine oxalate form of claim 15, wherein the crystalline form exhibits an XRPD pattern substantially the same as Figure 9.

19. The anhydrous tianeptine oxalate crystalline form of claim 4, wherein the crystalline form is tianeptine mono-oxalate Form B.

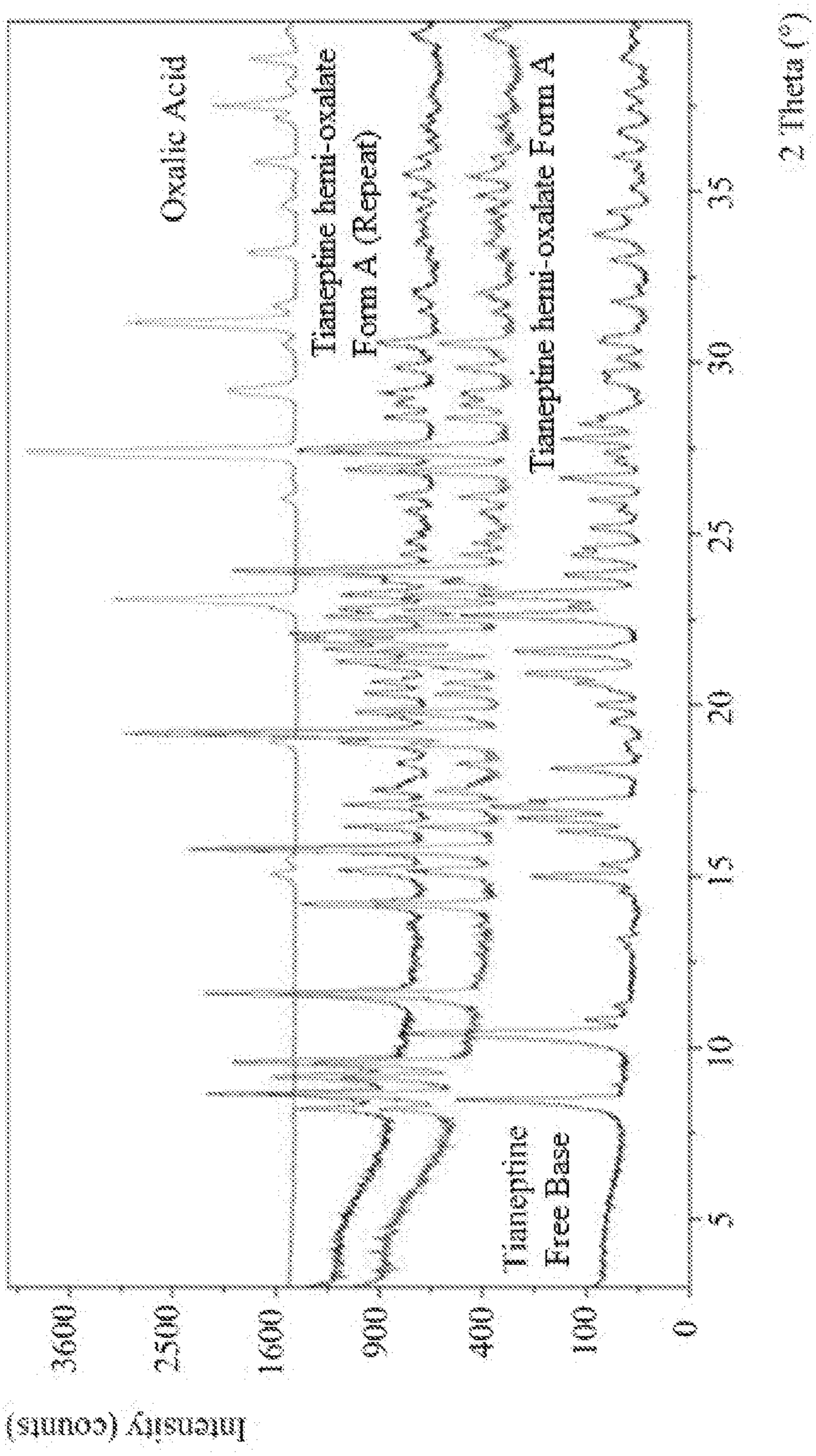
20. The anhydrous crystalline tianeptine oxalate form of claim 19, wherein the crystalline form exhibits an XRPD pattern substantially the same as Figure 14.

21. The pharmaceutical composition of claim 6, wherein the composition is in a solid form, a liquid form, a suspension form, a sustained release form, a delayed release form, or an extended release form.

22. The co-crystal of claim 3, wherein the co-crystal is a mixture of crystalline tianeptine hemi-oxalate Form A salt and tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or a combination thereof.

23. The co-crystal of claim 4, wherein the co-crystal is anhydrous crystalline tianeptine hemi-oxalate Form A, tianeptine mono-oxalate Form A, tianeptine mono-oxalate Form B, or a combination thereof.

Figure 1


Oxalic Acid
Tianeptine hemi-oxalate Form A (Repeat)
Tianeptine hemi-oxalate Form A
Tianeptine hemi-oxalate
Tianeptine Free Base
2 Theta (°)
Intensity (counts)
5
10
15
20
25
30
35
0
100
400
900
1600
2500
3600

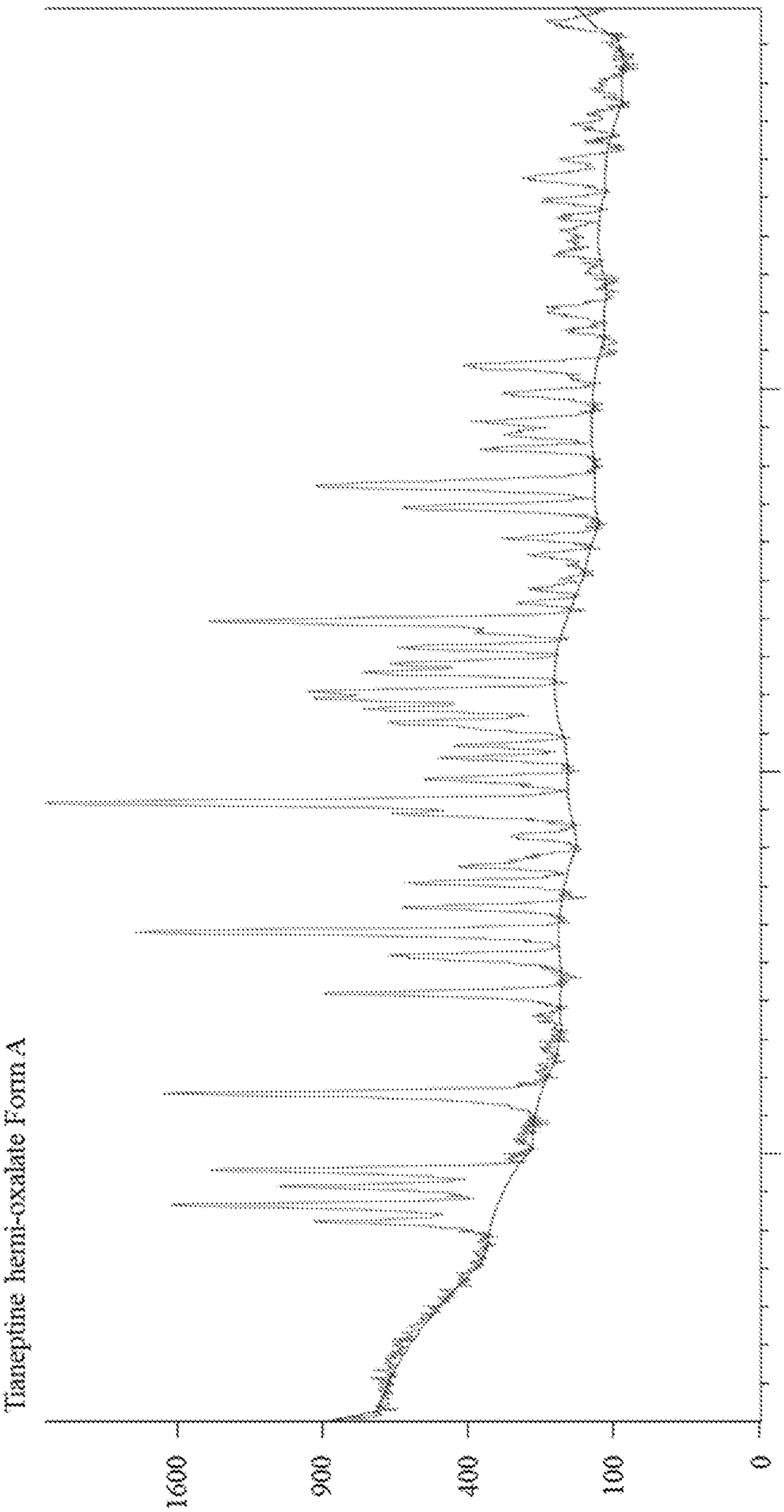

Position [°2Theta](Copper (Cu))
10
20
30
Timepine hemi-oxalate Form A
1600
800
400
100
0

Figure 2

Figure 3

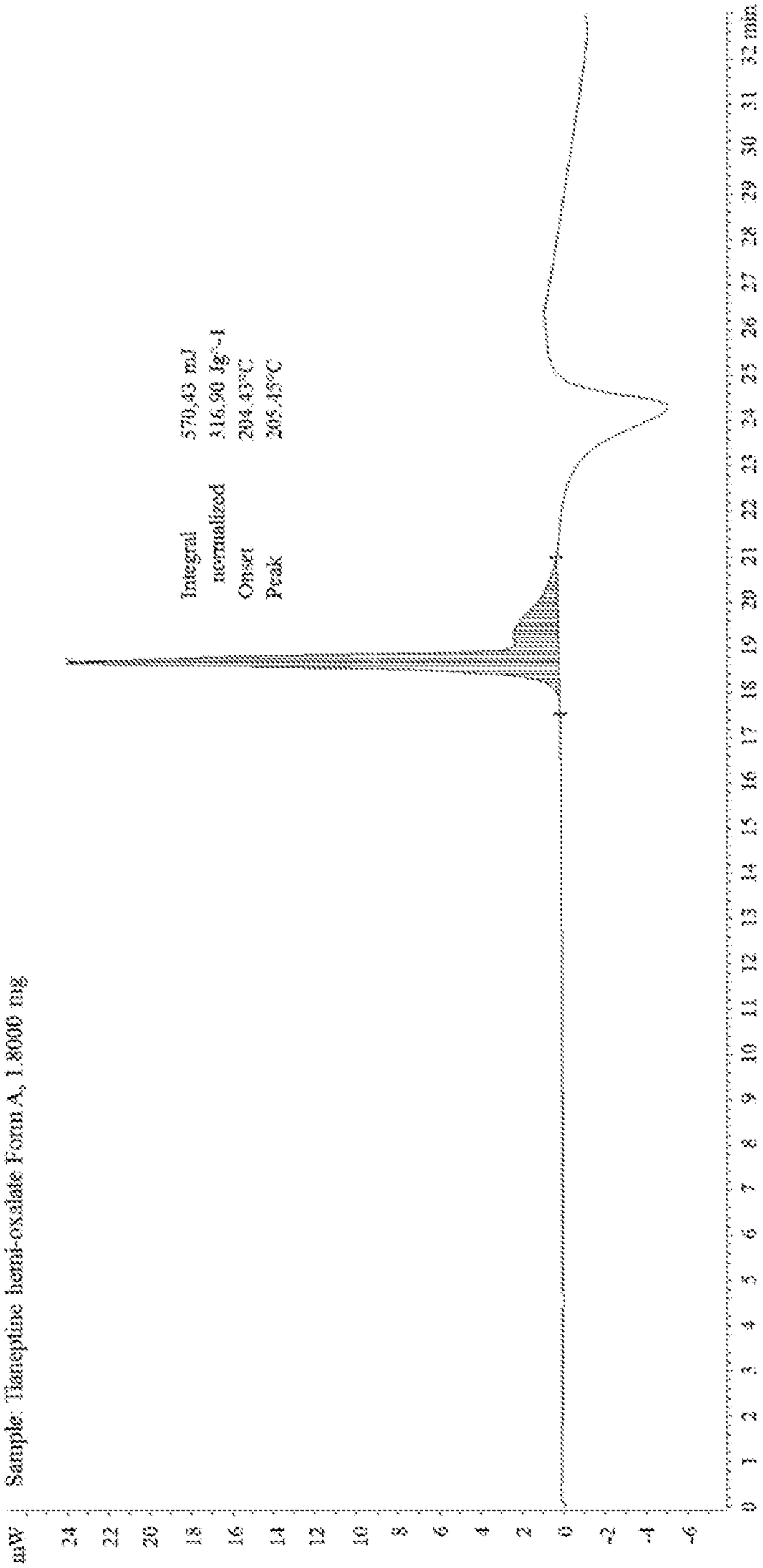

Integral 570,43 mJ
normalized 316,90 Jg^-1
Onset 204,43°C
Peak 209,45°C
Sample: Tianeptine hemi-oxalate Form A, 1.8000 mg
mW
min
°C

Figure 4

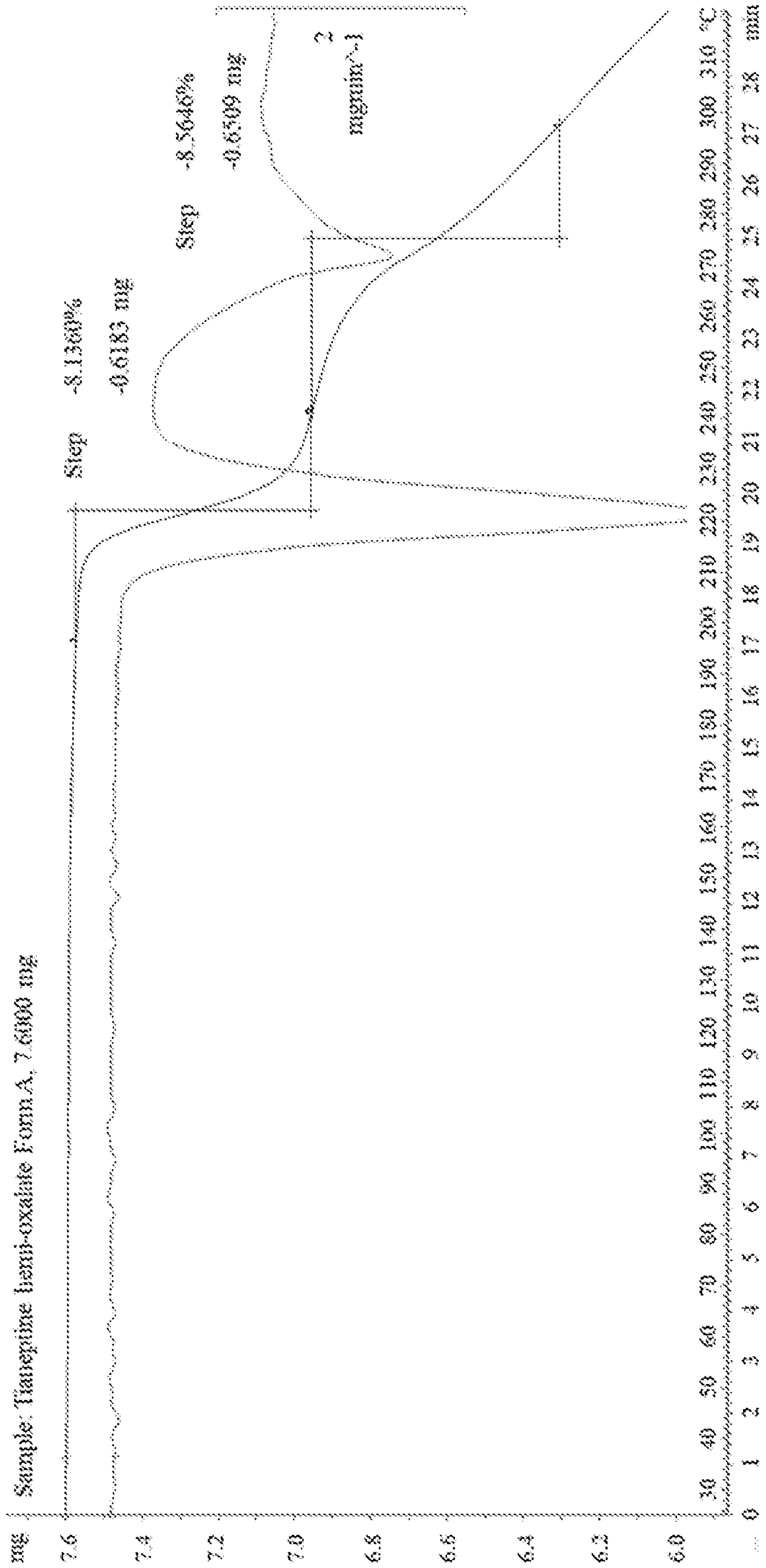
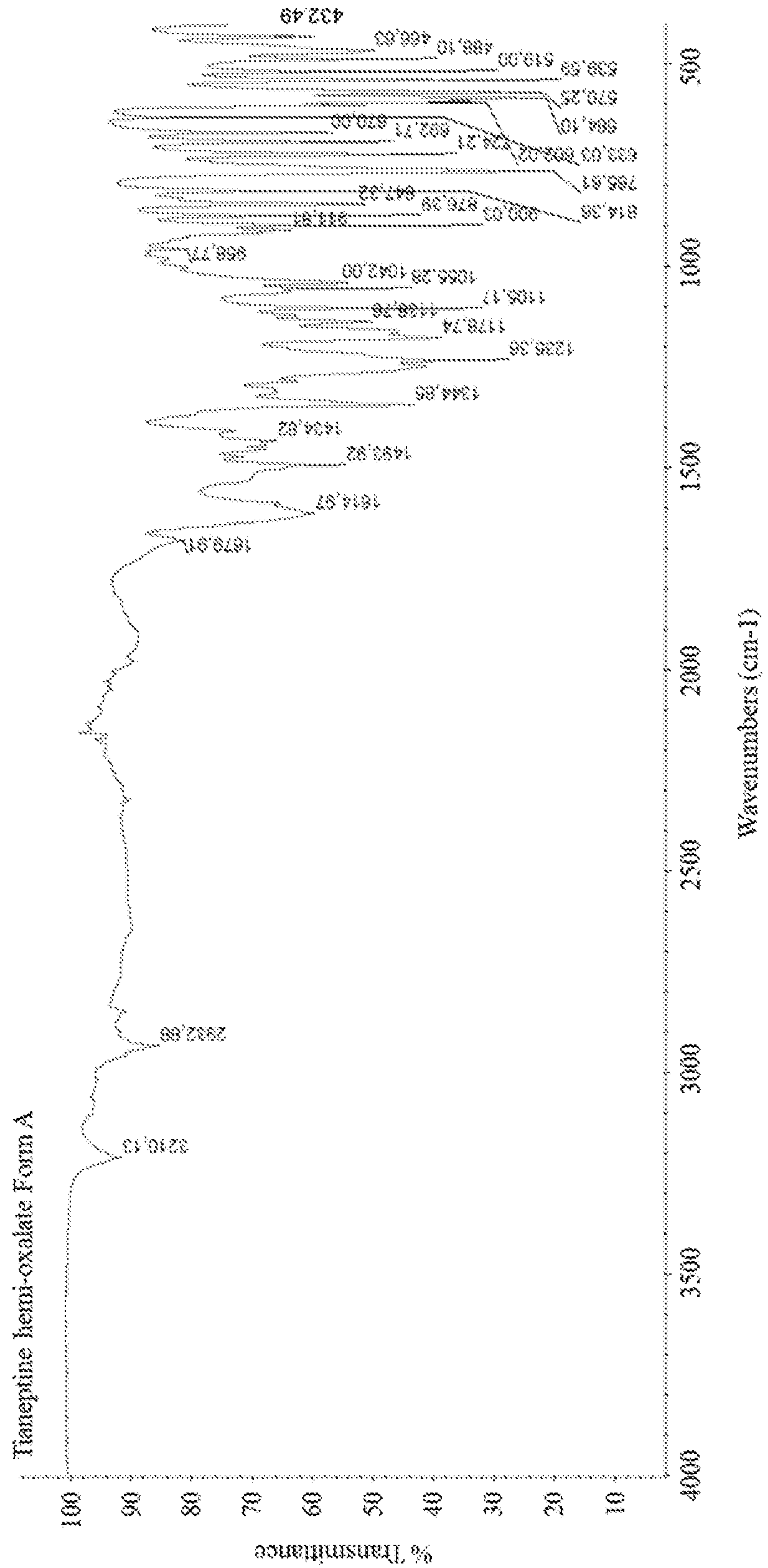

Sample: Tianeptine hemi-oxalate Form A, 7.6800 mg
mg
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 mm
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 °C
Step -8.5646%
-0.6509 mg
2 mg·min-1
Step -8.1368%
-0.6183 mg

Figure 5


Tianeptine hemi-oxalate Form A
% Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
500

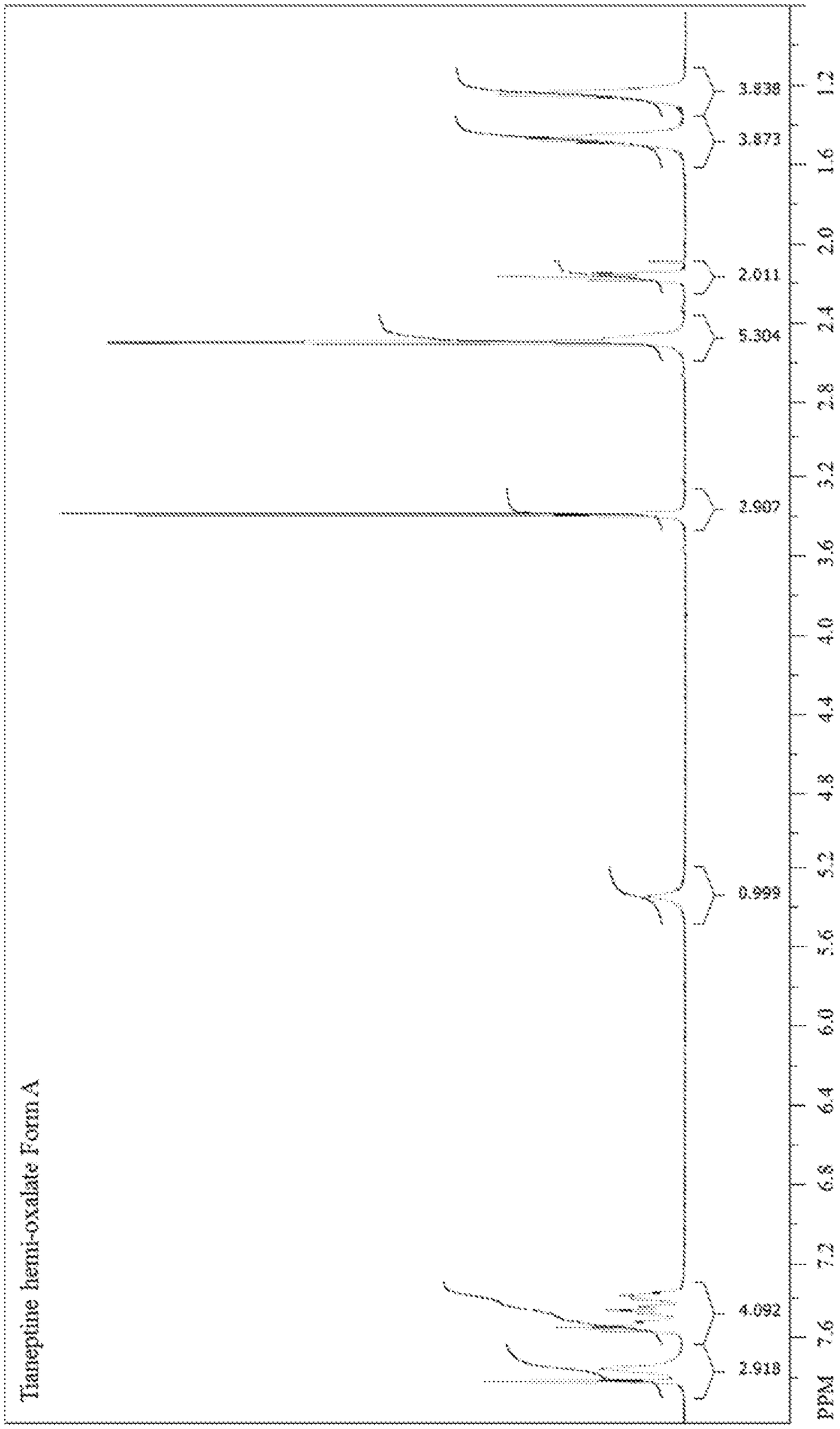

3.838
3.873
2.011
5.304
2.907
0.999
4.092
2.918
12
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
ppm
Tianeptine hemi-oxalate Form A

Figure 6

Figure 7

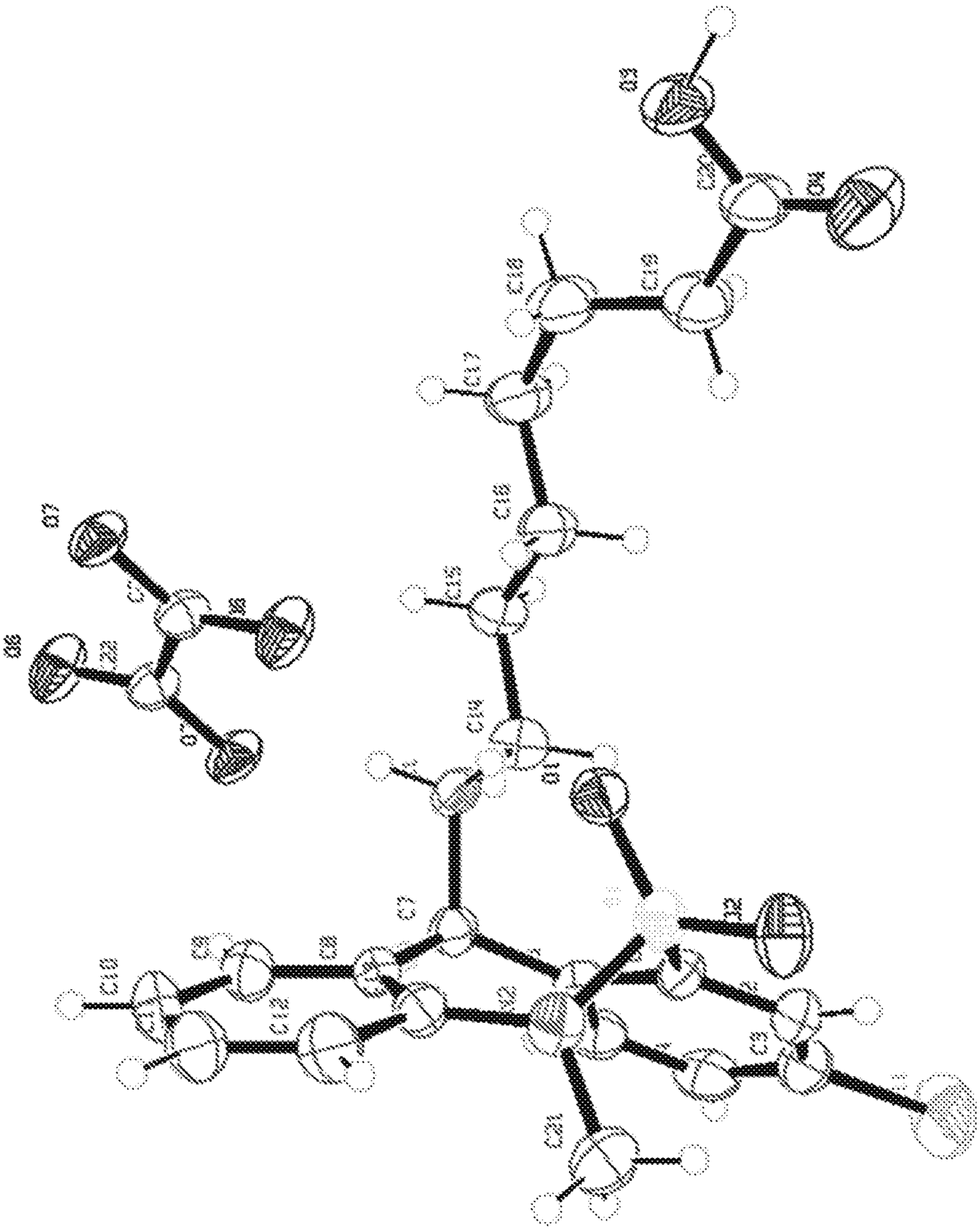

O7
C3
O4
O6
C2
C1
O5
C19
C18
C17
C16
C15
C14
C13
O3
O1
C8
C9
C10
C11
C12
O2

Figure 8

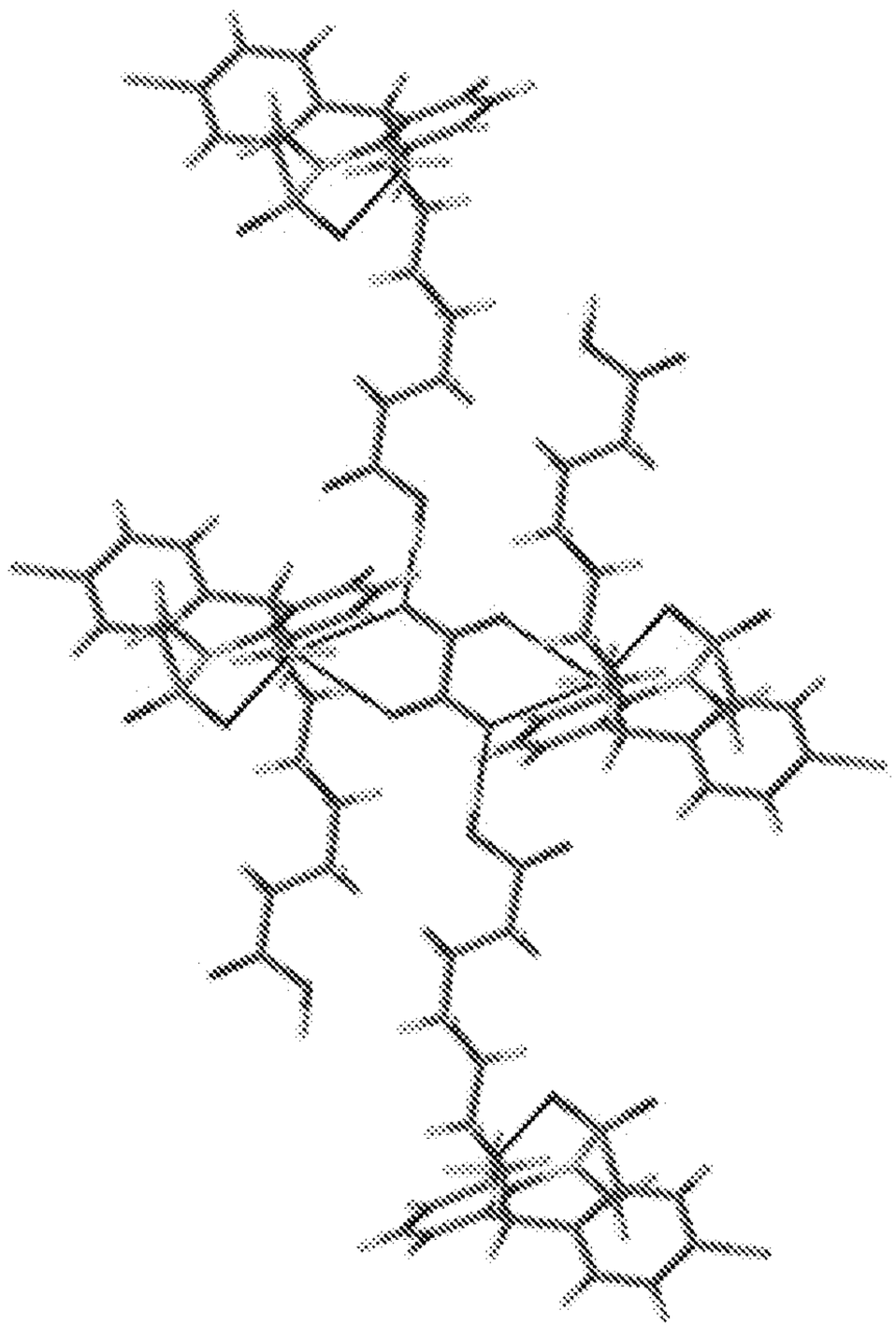


Figure 9

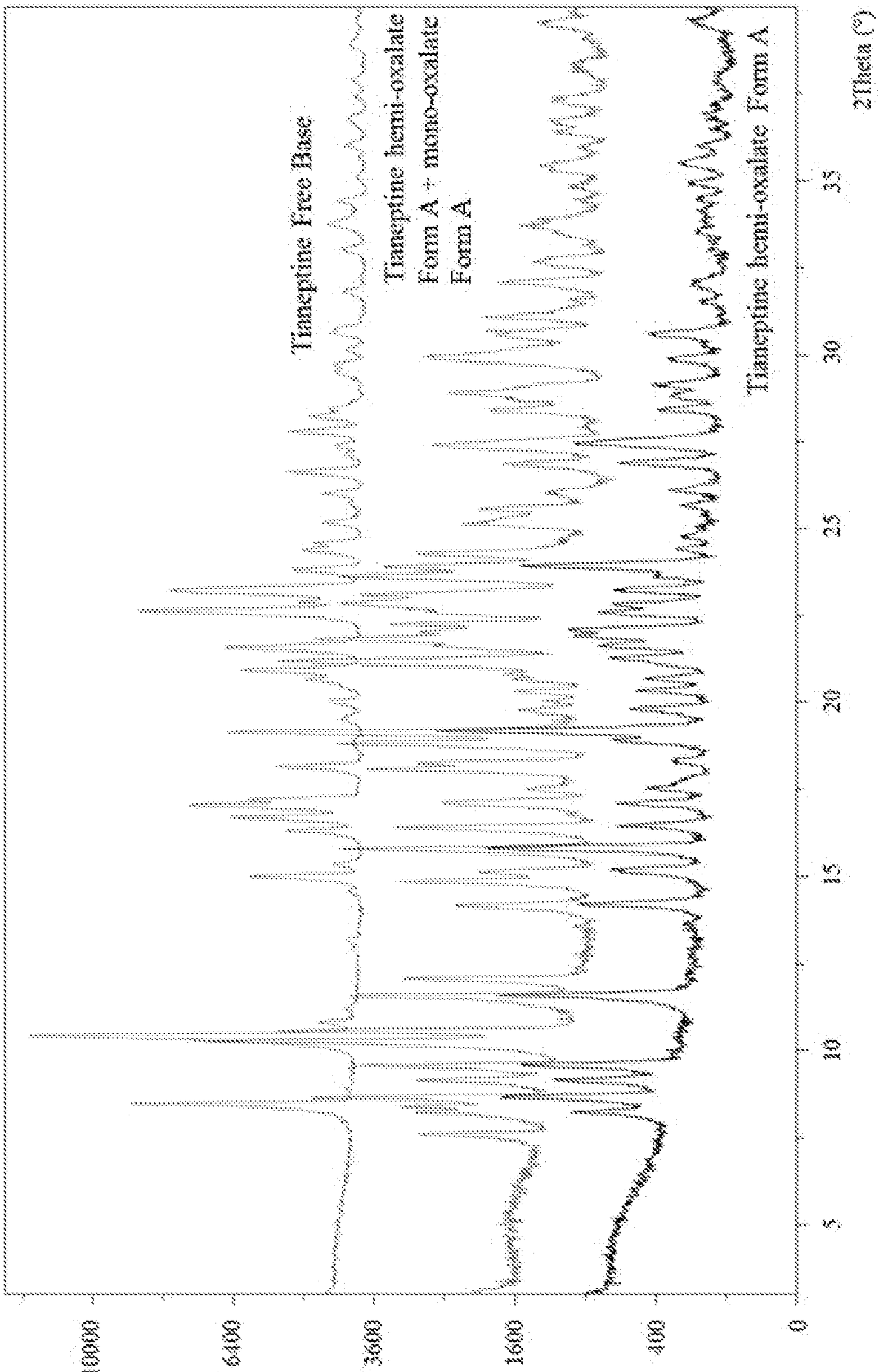

Intensity (counts)
0
400
800
1200
1600
2000
2400
2800
3200
3600
4000
4400
4800
5000
5200
5600
6000
6400
6800
7200
7600
8000
8400
8800
9200
9600
10000
5
10
15
20
25
30
35
2Theta (°)
Tianeptine Free Base
Tianeptine hemi-oxalate
Form A + mono-oxalate
Form A
Tianeptine hemi-oxalate Form A

Figure 10

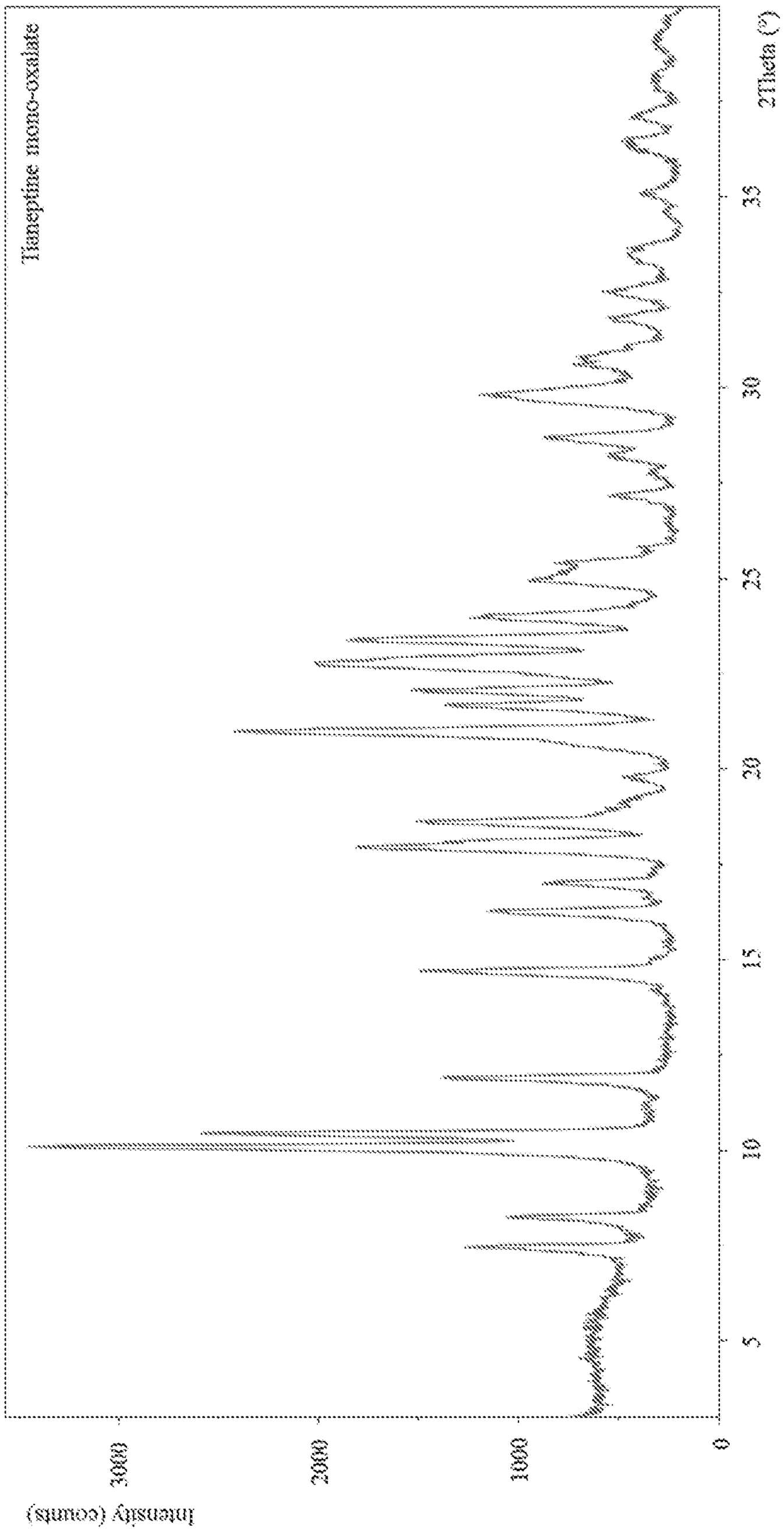

Tianeptine mono-oxalate
intensity (counts)
3000
2000
1000
0
5
10
15
20
25
30
35
2Theta (°)

Figure 11

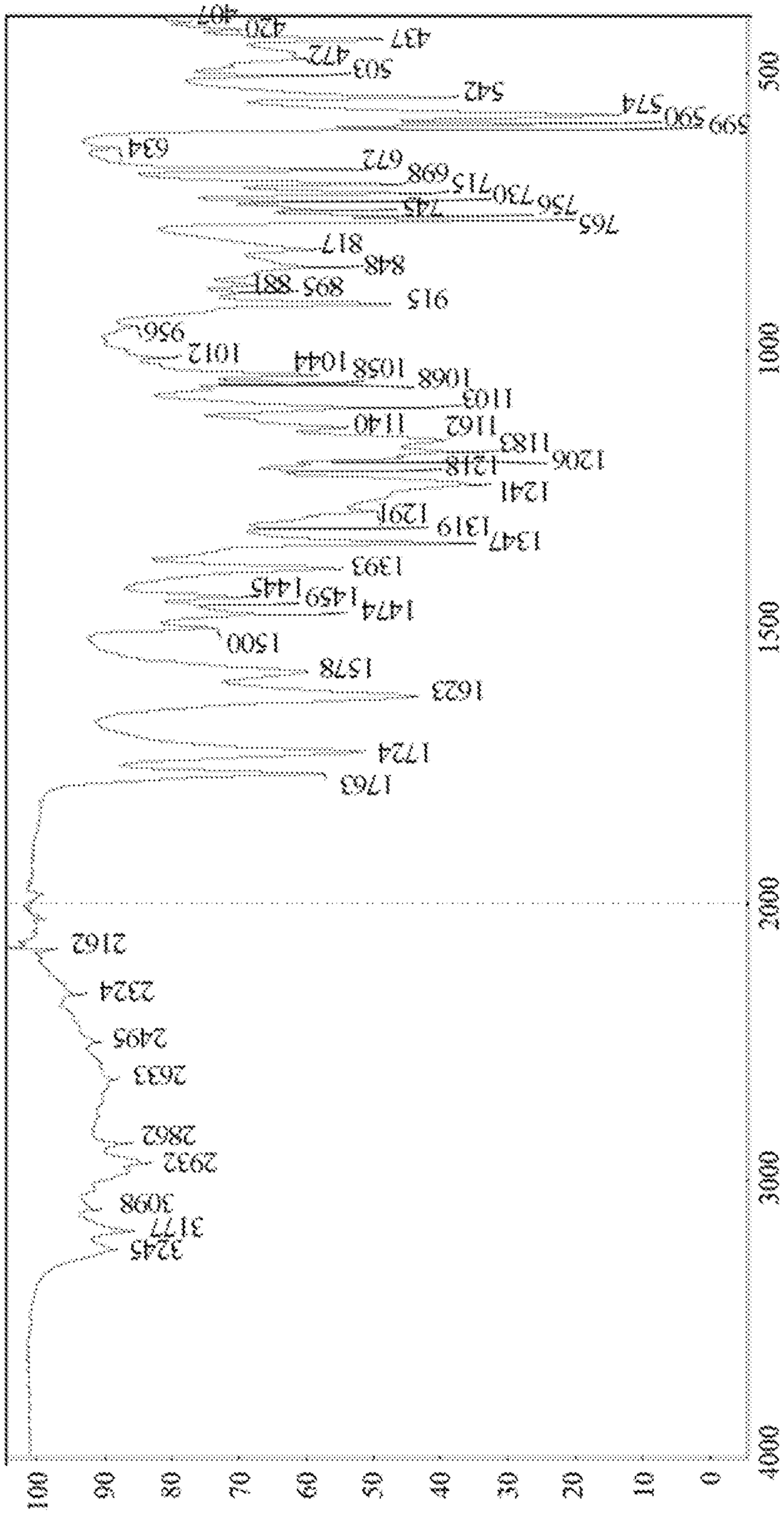
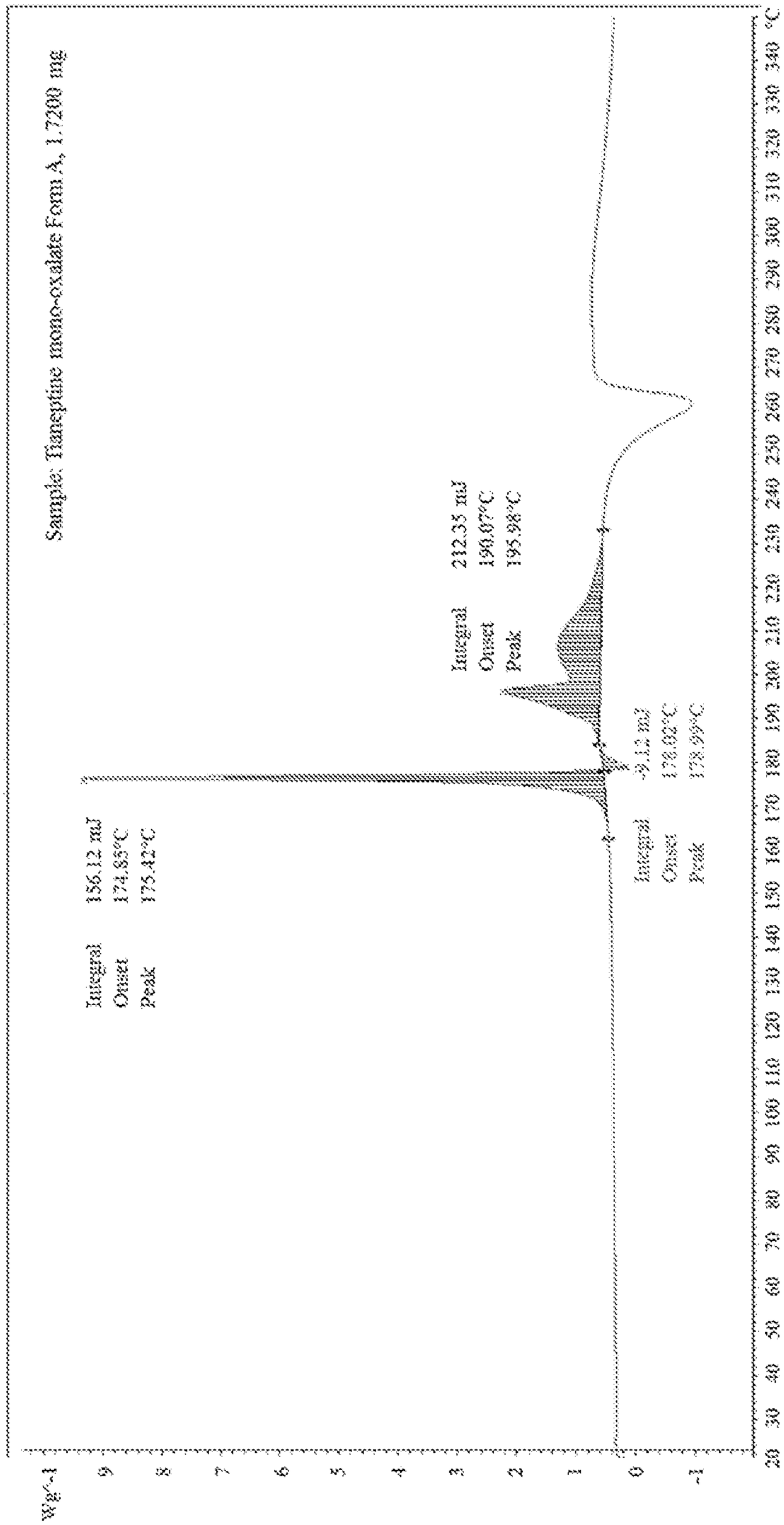

3005
2500
2000
1500
1000
500
Wavenumbers (cm-1)
% Transmittance
100
90
80
70
60
50
40
30
20
10
0
4
2162
2324
2495
2633
2862
2932
3098
3177
3245
1763
1724
1623
1578
1500
1474
1459
1445
1393
1347
1319
1291
1241
1206
1218
1183
1162
1140
1103
1068
1058
1044
1012
956
915
895
881
848
817
765
756
745
730
715
698
672
634
599
590
574
542
503
472
437
420
405

Figure 12


Sample: Tianeptine mono-oxalate Form A, 1.7200 mg
156.12 mJ
174.85°C
175.42°C
Integral
Onset
Peak
212.35 mJ
190.07°C
195.98°C
Integral
Onset
Peak
-9.12 mJ
176.02°C
178.99°C
150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 °C
150 140 130 120 110 100 90 80 70 60 50 40 30 20
9 8 7 6 5 4 3 2 1 0 -1
W/g ↓ exo

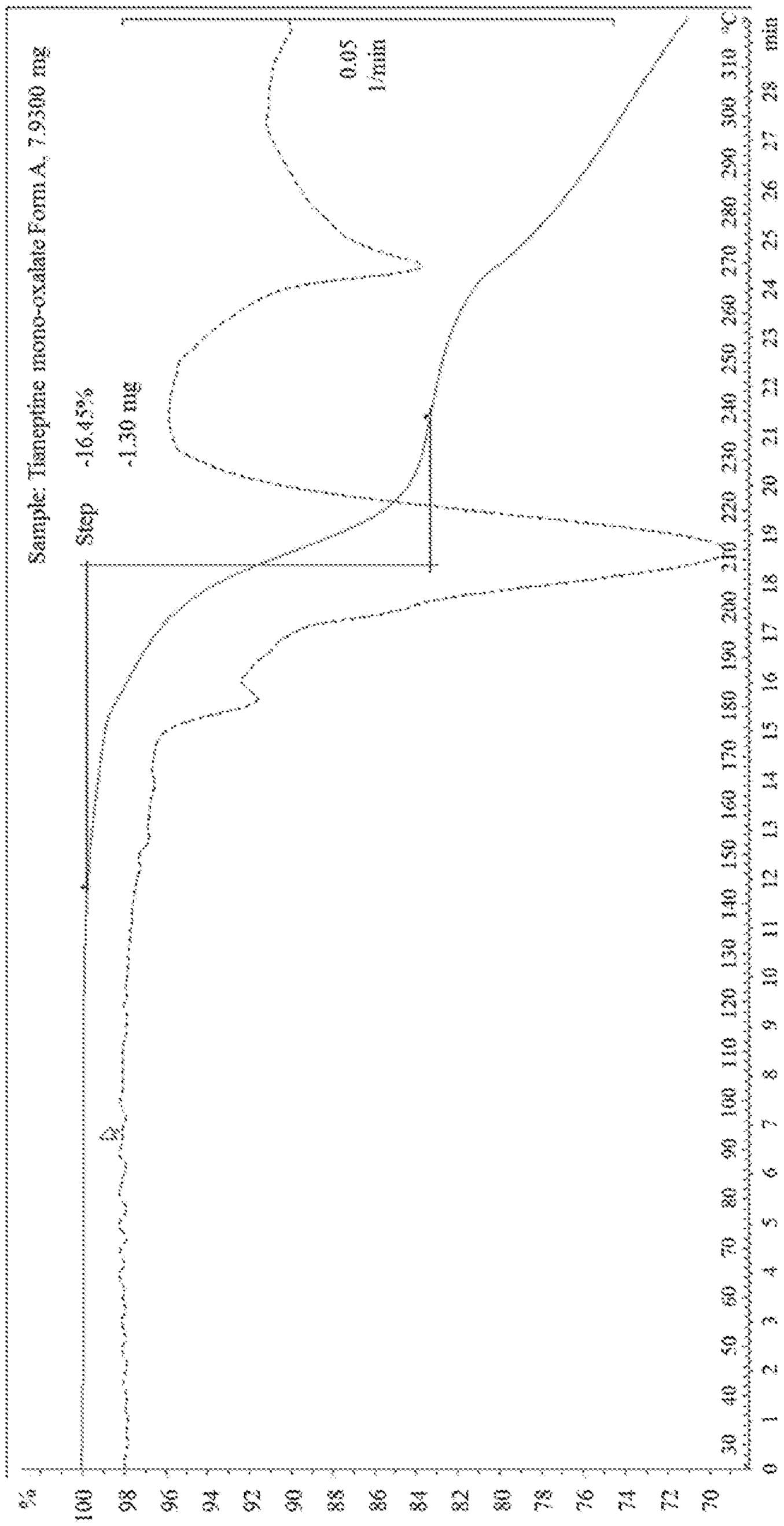

Sample: Tianeptine mono-oxalate Form A, 7.9300 mg
Step -16.45%
-1.30 mg
0.05
1/min
%
min
°C

Figure 13

Figure 14

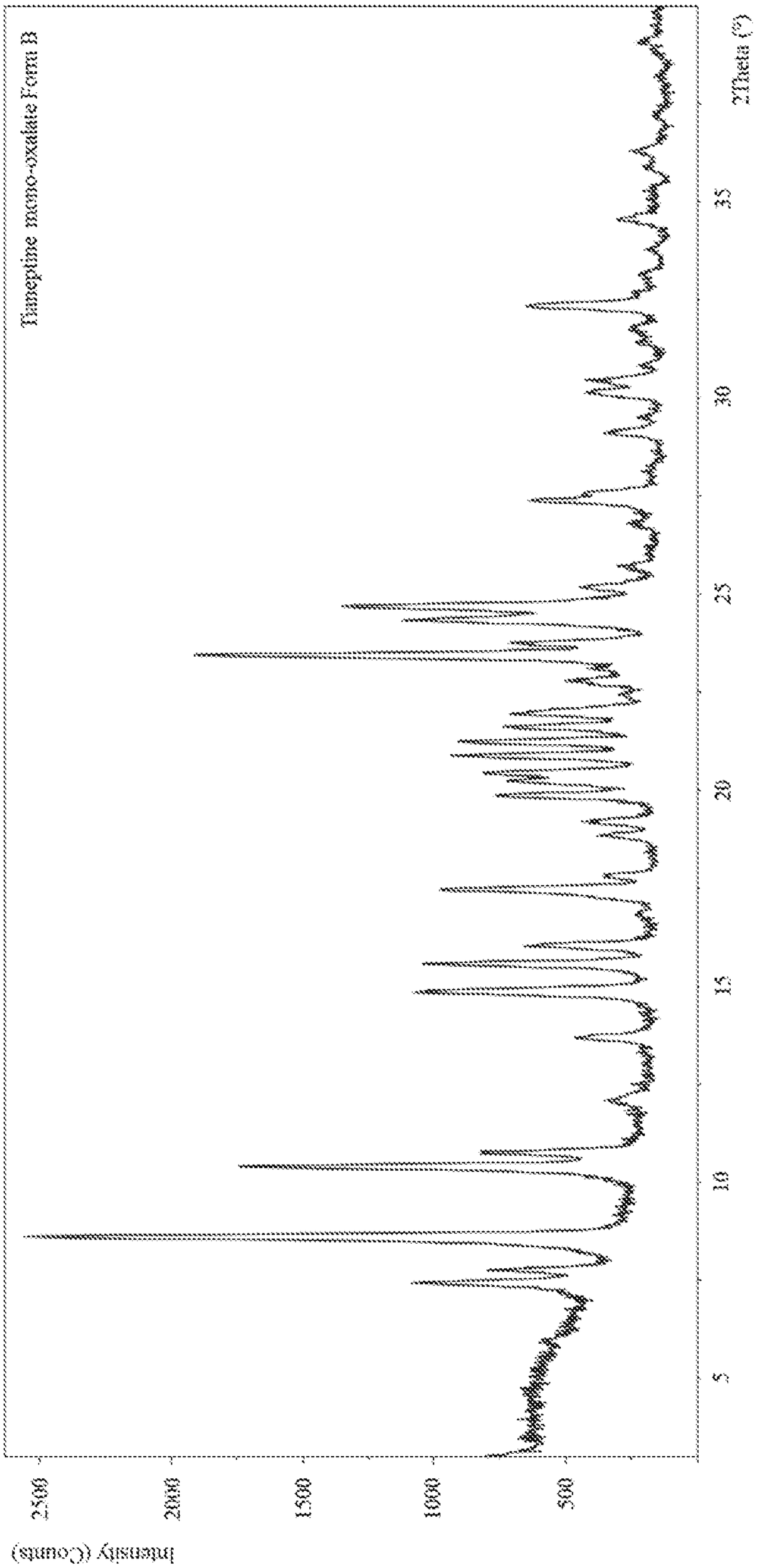

Tianeptine meso-oxalate Form B
Intensity (Counts)
2500
2000
1500
1000
500
5
10
15
20
25
30
35
2Theta (°)

Figure 15

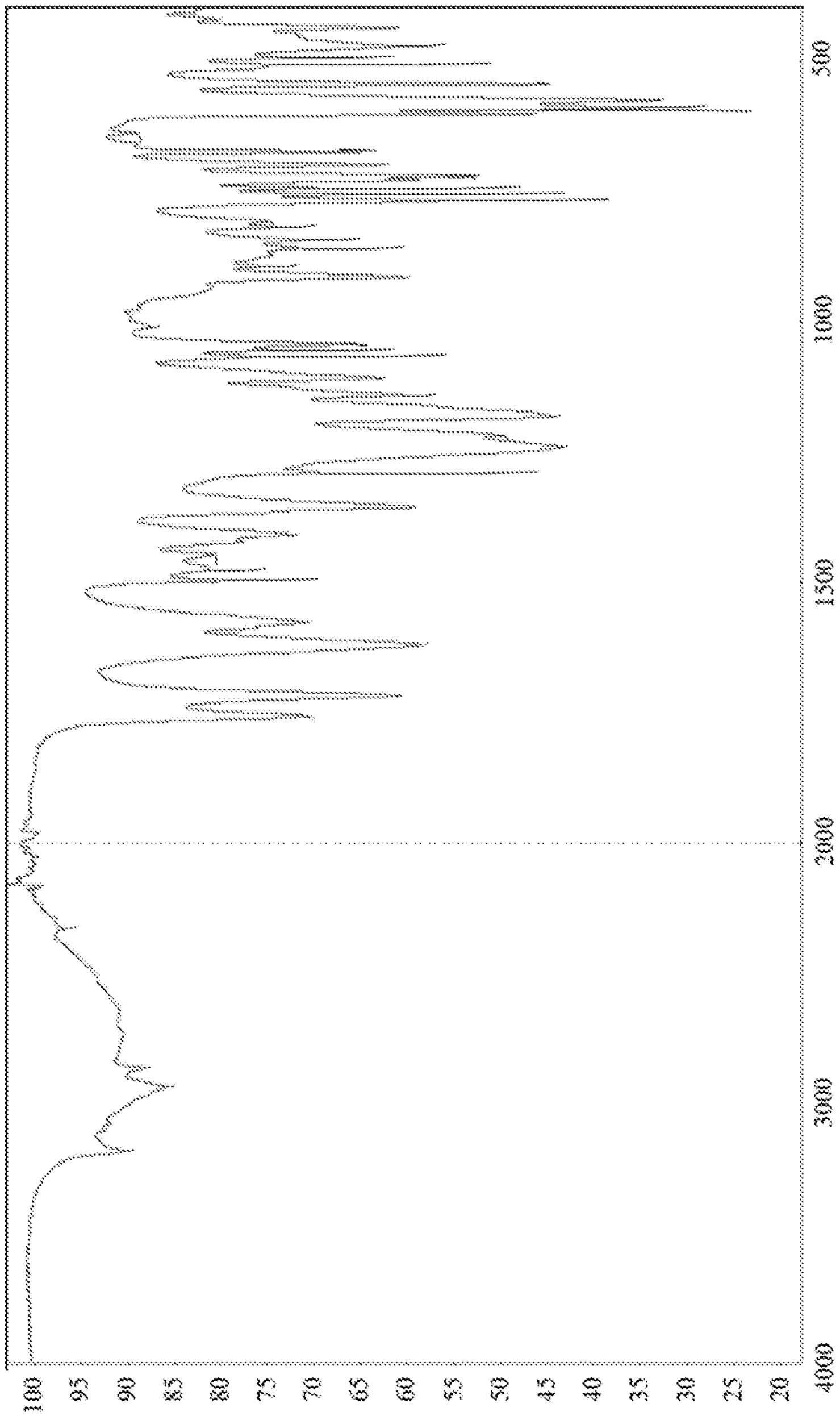

Tianeptine mono-oxalate Form B
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
4000
3000
2000
1500
1000
500
Wavenumbers (cm-1)

Figure 16

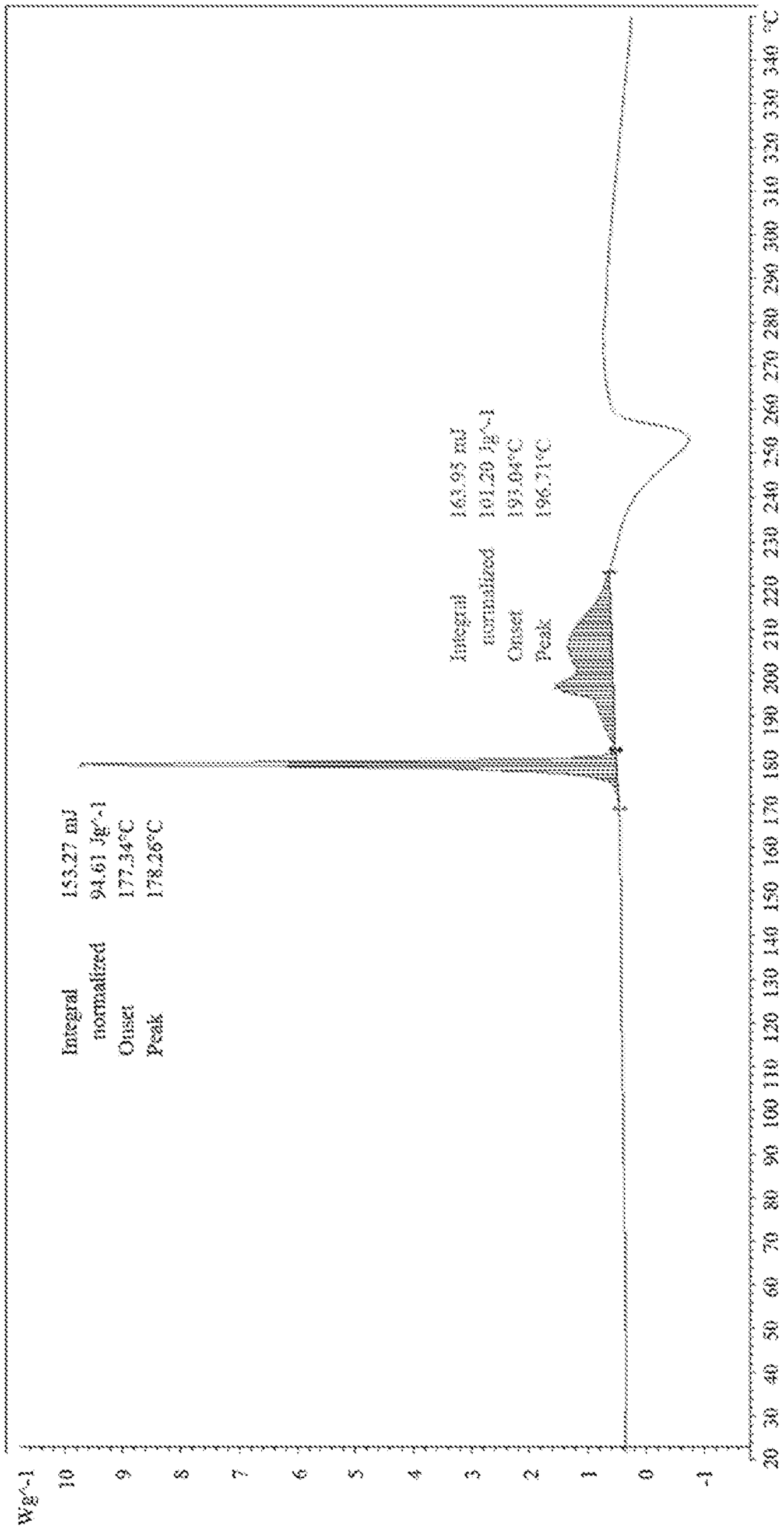
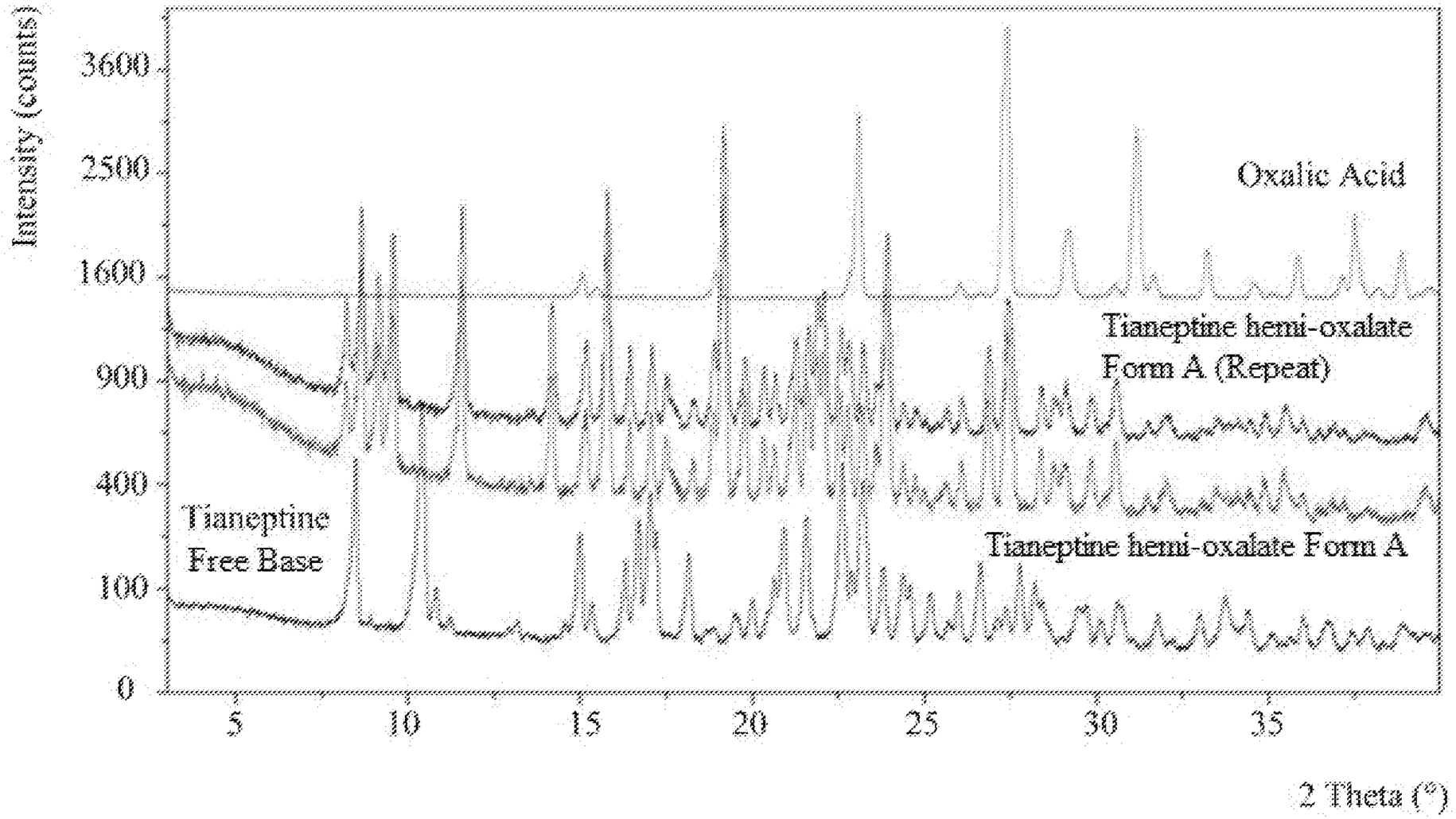
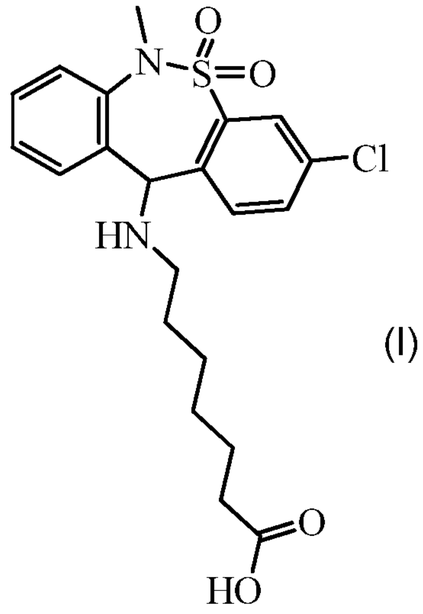

Tianeptine mono-oxalate Form B
W/g^-1
10
9
8
7
6
5
4
3
2
1
0
-1
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
310
320
330
340
°C
Integral 153.27 mJ
normalized 94.61 Jg^-1
Onset 177.34°C
Peak 178.26°C
Integral 163.95 mJ
normalized 101.20 Jg^-1
Onset 193.04°C
Peak 196.71°C

Figure 1


Intensity (counts)
3600
2500
1600
900
400
100
0
5
10
15
20
25
30
35
2 Theta (°)
Oxalic Acid
Tianeptine hemi-oxalate Form A (Repeat)
Tianeptine hemi-oxalate Form A
Tianeptine Free Base


N
S
O
O
Cl
HN
O
HO

(I)