



(86) Date de dépôt PCT/PCT Filing Date: 2015/06/18
 (87) Date publication PCT/PCT Publication Date: 2015/12/23
 (45) Date de délivrance/Issue Date: 2022/11/01
 (85) Entrée phase nationale/National Entry: 2016/12/16
 (86) N° demande PCT/PCT Application No.: US 2015/036347
 (87) N° publication PCT/PCT Publication No.: 2015/195862
 (30) Priorité/Priority: 2014/06/20 (US62/014,782)

(51) Cl.Int./Int.Cl. *C07D 498/04* (2006.01),
A61K 31/55 (2006.01)
 (72) Inventeur/Inventor:
HALL, MICHAEL L., US
 (73) Propriétaire/Owner:
CONSTELLATION PHARMACEUTICALS, INC., US
 (74) Agent: MARKS & CLERK

(54) Titre : FORMES CRISTALLINES DE L'ACETAMIDE 2-((4S)-6-(4-CHLOROPHENYL)-1-METHYL-4 H-BENZO [C] ISOXAZOLO [4S5-E] AZEPIN-4-YLE)
 (54) Title: CRYSTALLINE FORMS OF 2-((4S)-6-(4-CHLOROPHENYL)-1-METHYL-4H-BENZO[C]ISOXAZOLO[4,5-E]AZEPIN-4-YL)ACETAMIDE

(57) **Abrégé/Abstract:**

The present disclosure relates to a crystalline form of 2-((4S)-6-(4-chlorophenyl)-1- methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, which is useful as an inhibitor of bromodomain-containing proteins. The present disclosure also provides pharmaceutically acceptable compositions comprising the crystalline form and methods of using said compositions in the treatment of various disorders.

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

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



WIPO | PCT



(10) International Publication Number
WO 2015/195862 A8

(43) International Publication Date
23 December 2015 (23.12.2015)

- (51) International Patent Classification:
C07D 491/04 (2006.01) A61K 31/55 (2006.01)
- (21) International Application Number:
PCT/US2015/036347
- (22) International Filing Date:
18 June 2015 (18.06.2015)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
62/014,782 20 June 2014 (20.06.2014) US
- (71) Applicant: CONSTELLATION PHARMACEUTICALS, INC. [US/US]; 215 First Street, Suite 200, Cambridge, MA 02142 (US).
- (72) Inventor: HALL, Michael, L.; 155 Rosemont Street, Albany, NY 12206 (US).
- (74) Agents: DAVIS, Steven, G. et al.; Mccarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))

(48) Date of publication of this corrected version:

28 January 2016

(15) Information about Correction:

see Notice of 28 January 2016

(54) Title: CRYSTALLINE FORMS OF 2-((4S)-6-(4-CHLOROPHENYL)-1-METHYL-4H-BENZO[C]ISOXAZOLO[4,5-E]AZEPIN-4-YL)ACETAMIDE

(57) Abstract: The present disclosure relates to a crystalline form of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, which is useful as an inhibitor of bromodomain-containing proteins. The present disclosure also provides pharmaceutically acceptable compositions comprising the crystalline form and methods of using said compositions in the treatment of various disorders.



WO 2015/195862 A8

CRYSTALLINE FORMS OF 2-((4S)-6-(4-CHLOROPHENYL)-1-METHYL-4H-BENZO[C]ISOXAZOLO[4,5-E]AZEPIN-4-YL)ACETAMIDE

[0001]

TECHNICAL FIELD OF THE INVENTION

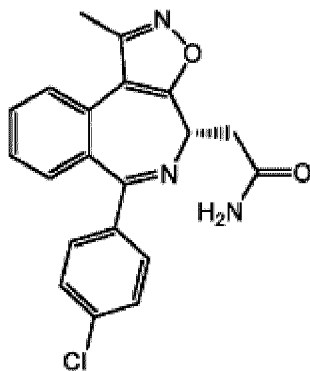
[0002] Provided herein is crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, processes for the preparing the crystalline form, pharmaceutical compositions comprising the crystalline form, and uses of the crystalline form and compositions thereof in treating bromodomain-containing protein-mediated disorders.

BACKGROUND OF THE INVENTION

[0003] Packaging the 3 billion nucleotides of the human genome into the nucleus of a cell requires tremendous compaction. To accomplish this feat, DNA in our chromosomes is wrapped around spools of proteins called histones to form dense repeating protein/DNA polymers known as chromatin: the defining template for gene regulation. Far from serving as mere packaging modules, chromatin templates form the basis of a newly appreciated and fundamentally important set of gene control mechanisms termed epigenetic regulation. By conferring a wide range of specific chemical modifications to histones and DNA, epigenetic regulators modulate the structure, function, and accessibility of our genome, thereby exerting a tremendous impact on gene expression. Hundreds of epigenetic effectors have recently been identified, many of which are chromatin-binding proteins or chromatin-modifying enzymes. Significantly, an increasing number of these proteins have been associated with a variety of disorders such as neurodegenerative disorders, metabolic diseases, inflammation, and cancer. Thus, highly selective therapeutic agents directed against this emerging class of gene regulatory proteins promise new approaches to the treatment of human diseases.

[0004] 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is an inhibitor of one or more bromodomain-containing proteins and is useful in treating bromodomain-containing protein-mediated disorders, such as, e.g., proliferative disorders, inflammatory diseases, sepsis, autoimmune diseases, and viral infections. The

amorphous form of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is exemplified in U.S. Patent Publication No. 2012/0157428 as Compound 144. 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is represented by the following structural formula:



[0005] Given the therapeutic benefits associated with the amorphous form of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, development of other forms of this compound, having improved properties, represents an attractive area for producing enhanced formulations for inhibition of one or more bromodomain-containing proteins.

SUMMARY OF THE INVENTION

[0006] Provided herein is a novel crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, which has improved properties and displays advantageous characteristics over the prior disclosed amorphous form. As described in detail below, such advantages include e.g., improved relative humidity stability, ease of isolation, favorable pharmacokinetic parameters, and process reproducibility of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0007] Also provided herein is a novel hydrated (e.g., monohydrate) crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0008] Further provided herein are pharmaceutical compositions comprising crystalline and hydrated crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, methods for their manufacture, and uses thereof for treating bromodomain-containing protein-mediated disorders, such as, e.g., proliferative disorders, inflammatory diseases, sepsis, autoimmune diseases, and viral infections.

BRIEF DESCRIPTION OF THE FIGURES

[0009] Figure 1 depicts an X-ray powder diffraction pattern (XRPD) for monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0010] Figure 2 depicts a ¹³C-NMR profile for monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0011] Figure 3 depicts a thermal gravimetric analysis (TGA) pattern for monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0012] Figure 4 depicts a gravimetric moisture sorption curve for monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0013] Figure 5 depicts a Differential Scanning Calorimetry (DSC) spectrum for monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0014] Figure 6 depicts a gravimetric moisture sorption curve for amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0015] Figure 7 depicts Individual Plasma Concentration vs. time in male Sprague Dawley rats after oral administration with monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in 0.5% MC at 10 and 60 mg/kg.

[0016] Figure 8 depicts Individual Plasma Concentration vs. time in Male Beagle Dogs after Oral Administration with amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in 0.5% MC at 2 mg/kg.

[0017] Figure 9 depicts Individual Plasma Concentration vs. time in Male Beagle Dogs after Oral Administration with monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in 0.5% MC at 2 mg/kg.

[0018] Figure 10 depicts an X-ray powder diffraction pattern (XRPD) for GMP scale up of monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0019] Figure 11 depicts a Differential Scanning Calorimetry (DSC) spectrum for GMP scale up of monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0020] Figure 12 depicts a thermal gravimetric analysis (TGA) pattern for GMP scale up of monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

DETAILED DESCRIPTION

Definitions

[0021] When used alone, the term “Form A” refers to the crystalline polymorph Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. The terms “Form A”, “Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide”, and “crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide” are used interchangeably. The terms “Form A”, “Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide”, and “crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide” are intended to include hydrated and solvated forms of the crystalline polymorph Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide as well as anhydrous forms. Such forms are characterized e.g., by XRPD. “Anhydrous” as used herein, means that the crystalline form comprises substantially no water in the crystal lattice e.g., less than 1% by weight as determined by Karl Fisher analysis.

[0022] When used alone, the term “monohydrate Form A” refers to the monohydrate crystalline polymorph Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. The terms “monohydrate Form A”, “monohydrate crystalline Form A”, and “monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide are used interchangeably. Monohydrate Form A is characterized e.g., by XRPD together with Karl Fisher titration analysis.

[0023] The term “amorphous” means a solid that is present in a non-crystalline state or form. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. Solid state ordering of solids may be determined by standard techniques known in

the art, e.g., by X-ray powder diffraction (XRPD) or differential scanning calorimetry (DSC). Amorphous solids can also be differentiated from crystalline solids e.g., by birefringence using polarized light microscopy.

[0024] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not adversely affect the pharmacological activity of the compound with which it is formulated, and which is also safe for human use. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, magnesium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances (e.g., microcrystalline cellulose, hydroxypropyl methylcellulose, lactose monohydrate, sodium lauryl sulfate, and crosscarmellose sodium), polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Description of Exemplary Compounds

[0025] In one aspect, the present disclosure provides crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0026] In one aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is characterized by at least three, at least four, at least five, or by six x-ray powder diffraction peaks at 2Θ angles selected from 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° . Alternatively, crystalline Form A is characterized by x-ray powder diffraction peaks at 2Θ angles 4.73° , 9.42° , 12.91° , 18.09° , 18.48° , 18.80° , 19.70° , 21.42° , and 25.17° . In another alternative crystalline Form A is characterized by x-ray powder diffraction peaks at 2Θ angles 4.73° , 8.11° , 9.42° , 12.91° , 14.10° , 14.97° , 18.09° , 18.48° , 18.80° , 19.70° , 21.42° , and 25.17° , 26.07° , and 26.53° .

[0027] In another aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has an XRPD pattern that is substantially the same XRPD pattern shown in Figure 1.

[0028] In another aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has an XRPD pattern that is substantially the same XRPD pattern shown in Figure 10.

[0029] In another aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has an XRPD pattern that substantially includes the peaks in Table 2.

[0030] In another aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has an XRPD pattern that substantially includes the peaks in Table 3.

[0031] In another aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is characterized by ¹³C-NMR peaks at 171.3, 168.6, 167.4, 139.30, 134.7, 133.4, 131.4, 131.1, 130.7, 130.0, 128.0, 126.8, 125.8, 112.55, 55.9, 53.5, 36.4, 18.5, and 10.6 in DMSO-d₆ with 0.05% tetramethylsilane. Alternatively, crystalline Form A is characterized by a ¹³C-NMR pattern that is substantially the same ¹³C-NMR pattern shown in Figure 2.

[0032] In one aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has a TGA pattern that is substantially the same TGA pattern shown in Figure 3. Alternatively, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has a TGA pattern that is substantially the same TGA pattern shown in Figure 12.

[0033] In one aspect, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has a DSC pattern that is substantially the same DSC pattern shown in Figure 5. Alternatively, crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has a DSC pattern that is substantially the same DSC pattern shown in Figure 11.

[0034] In one aspect, the crystalline forms recited in the preceding paragraphs represent a hydrated crystalline Form A (e.g., monohydrate Form A) of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0035] In one aspect, the hydrated crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is a monohydrate characterized by at least three, at least four, at least five, or by six x-ray powder diffraction peaks at 2 θ angles selected from 4.73°, 18.09°, 18.48°, 18.80°, 19.70°, and 25.17°; optionally together

with one or both of the TGA and DSC parameters recited above; and a Karl Fisher titration water composition range of 4 to 5 wt%.

[0036] It will be understood that the 2-theta values of the X-ray powder diffraction patterns for monohydrate crystalline Form A may vary slightly from one instrument to another and also depending on variations in sample preparation and batch to batch variation. For example, without wishing to be bound by theory, it is believed that some variations in 2-theta values are attributable to the amount of water comprised in the crystalline lattice, e.g., in the case of hydrated (such as a monohydrate) and anhydrous forms. Therefore, the XRPD patterns / assignments for crystalline Form A are not to be construed as absolute and can vary ± 0.2 degrees, except for the 2Θ angles 8.11° , 14.10° , 14.97° , 26.07° , and 26.53° of crystalline Form A, which can vary by ± 0.3 degrees.

[0037] As intended herein, "substantially the same XRPD pattern as shown in Figure 1" and "substantially the same XRPD pattern as shown in Figure 10" means that for comparison purposes, at least 90% of the peaks shown in Figure 1 and Figure 10 are present. It is to be further understood that for comparison purposes some variability in peak intensities from those shown in Figure 1 and Figure 10 are allowed, such as ± 0.2 degrees, except for the 2Θ angles 8.11° , 14.10° , 14.97° , 26.07° , and 26.53° of crystalline Form A, which can vary by ± 0.3 degrees.

[0038] It will also be understood that the chemical shifts of the NMR patterns for the monohydrate crystalline Form A may vary slightly from one instrument to another and also depending on variations in sample preparation and batch to batch variation. Therefore, the NMR chemical shifts, patterns, and/or assignments for monohydrate crystalline Form A are not to be construed as absolute and can vary ± 0.2 ppm.

[0039] In one aspect, the present disclosure provides a process for preparing crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. Such a process includes, e.g., forming crystalline Form A from a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and water; or forming crystalline Form A from a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a combination of water and organic solvent. In one aspect, crystalline Form A is precipitated from a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a

combination of water and organic solvent. In one aspect, the processes described above results in the formation of monohydrate crystalline Form A.

[0040] Acceptable solvent mixtures for the aforementioned processes include, e.g., ethanol/water, isopropanol/water, tetrahydrofuran/water, acetone/water, methanol/water, and acetonitrile/water. In one aspect, the process described herein comprises formation of monohydrate crystalline Form A from amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in a 60:40 mixture of ethanol/water.

[0041] Processes for preparing crystalline Form A also include seeding a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and water with crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide; or seeding a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a combination of water and organic solvent with crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. In one aspect, the seeding is done with monohydrate crystalline Form A to prepare the resulting monohydrate form. Processes for preparing crystalline Form A and the specific monohydrate crystalline Form A can also be achieved upon suspending amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in water, absent seeding.

[0042] Acceptable solvent mixtures for the process mention in the two preceding paragraphs also include, e.g., ethanol/water, isopropanol/water, tetrahydrofuran/water, acetone/water, methanol/water, and acetonitrile/water. In one aspect, the process described herein comprises formation of monohydrate crystalline Form A from seeding amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide with crystalline monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in a 60:40 mixture of ethanol/water.

Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[0043] According to other aspects, the present disclosure relates to a method of inhibiting a bromodomain-containing protein (such as a BET protein, e.g., BRD2, BRD3, BRD4, and/or BRDT) using a composition comprising crystalline Form A described herein and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of the crystalline form

in a provided composition is such that is effective to measurably inhibit one or more bromodomain-containing proteins (such as a BET protein, *e.g.*, BRD2, BRD3, BRD4, and/or BRDT), or a mutant thereof, in a biological sample or in a patient. In certain aspects, the amount of the crystalline form in a provided composition is such that is effective to measurably inhibit one or more bromodomain-containing proteins (such as a BET protein, *e.g.*, BRD2, BRD3, BRD4, and/or BRDT), or a mutant thereof, in a biological sample or in a patient. In certain aspects, a provided composition is formulated for administration to a patient in need of such composition. In some aspects, a provided composition is formulated for oral administration to a patient.

[0044] Compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

[0045] Other forms of administration are as described in U.S. Patent Publication No. 2012/0157428. Dosage forms for oral administration are also as described in U.S. Patent Publication No. 2012/0157428.

[0046] The amount of provided crystalline form that may be combined with carrier materials to produce a composition in a single dosage form will vary depending upon the patient to be treated and the particular mode of administration. Provided compositions may be formulated such that a dosage of between 0.001 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0047] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of a provided crystalline form in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[0048] Crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and compositions described herein are generally useful for the inhibition of activity of one or more proteins involved in epigenetic regulation *e.g.*, as those described in U.S. Patent Publication No. 2012/0157428. Thus, in

some aspects, the present disclosure provides a method of inhibiting one or more proteins involved in epigenetic regulation, such as proteins containing acetyl-lysine recognition motifs, also known as bromodomains (*e.g.*, BET proteins, such as BRD2, BRD3, BRD4, and/or BRDT), by administering a provided crystalline form or composition.

[0049] The present disclosure also relates to treating MYC-dependent cancers, inflammatory diseases, and viral diseases (*e.g.*, as those described in U.S. Patent Publication No. 2012/0157428), comprising administering one or more of the compounds described herein.

[0050] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein.

[0051] Diseases and conditions treatable according to the methods described herein include, but are not limited to, cancer and other proliferative disorders, inflammatory diseases, sepsis, autoimmune disease, and viral infection. Thus, one aspect is a method of treating a subject having a disease, disorder, or symptom thereof the method including administration of a crystalline form or composition herein to the subject. In one aspect, a human patient is treated with a crystalline form described herein and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said crystalline form is present in an amount to measurably inhibit bromodomain-containing protein activity (such as BET protein, *e.g.*, BRD2, BRD3, BRD4, and/or BRDT) in the patient.

[0052] The present disclosure further relates to a method for treating or ameliorating cancer or another proliferative disorder by administration of an effective amount of a crystalline form as described herein to a mammal, in particular a human in need of such treatment. In some aspects, the disease to be treated is cancer. Examples of cancers treated include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma,

atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central

nervous system lymphoma, primary effusion lymphoma, primary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0053] In some aspects, the present disclosure provides a method of treating a benign proliferative disorders, infectious and noninfectious inflammatory events and autoimmune and other inflammatory diseases, systemic inflammatory response syndromes, and viral infections, e.g., those as described in U.S. Patent Publication No. 2012/0157428.

[0054] The present disclosure further provides a method of treating a subject, such as a human, suffering from one of the abovementioned conditions, illnesses, disorders or diseases. The method comprises administering a therapeutically effective amount of crystalline Form A, which functions by inhibiting a bromodomain and, in general, by modulating gene expression, to induce various cellular effects, in particular induction or repression of gene expression, arresting cell proliferation, inducing cell differentiation and/or inducing apoptosis, to a subject in need of such treatment.

[0055] The present disclosure further relates to the use of a provided crystalline form for the production of pharmaceutical compositions which are employed for the treatment and/or amelioration of the diseases, disorders, illnesses and/or conditions as mentioned herein.

[0056] Another aspect of the present disclosure is the use of the crystalline form as described herein in the manufacture of a medicament for use in the treatment of a disorder or disease herein. Another object of the present disclosure is the use of the crystalline form as described herein for use in the treatment of a disorder or disease herein.

[0057] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition may also be present in the compositions of this disclosure or administered separately as a part of a dosage

regimen. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[0058] The disclosed crystalline form may also be used in combination with one or more antiproliferative compounds or other additional compounds, e.g., as described in U.S. Patent Publication No. 2012/0157428.

[0059] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with the present disclosure. For example, a provided crystalline form may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, one aspect provides a single unit dosage form comprising a provided crystalline form, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle for use in the methods of the disclosure.

EXEMPLIFICATION

[0060] As depicted in the Examples below, in certain exemplary embodiments, crystalline Form A is prepared according to the following general procedures.

[0061] XRPD analyses were conducted using a CubiX-Pro XRD operating with a Cu radiation source at 45 kV, 40 mA. Samples were placed on Si zero-return sample holders and analysis was performed using a 10 mm irradiated width. The scanning parameters were from a range of 3.0 to 45.0° with a step size of 0.02°, 10 seconds per step, and an active length of 2.54°. Peak assignments were performed using X’Pert HighScore Plus software with the following parameters: Fixed Divergence Slit Size, 1.00°, 1.59 mm and Crossover Point, 44.3°Omega.

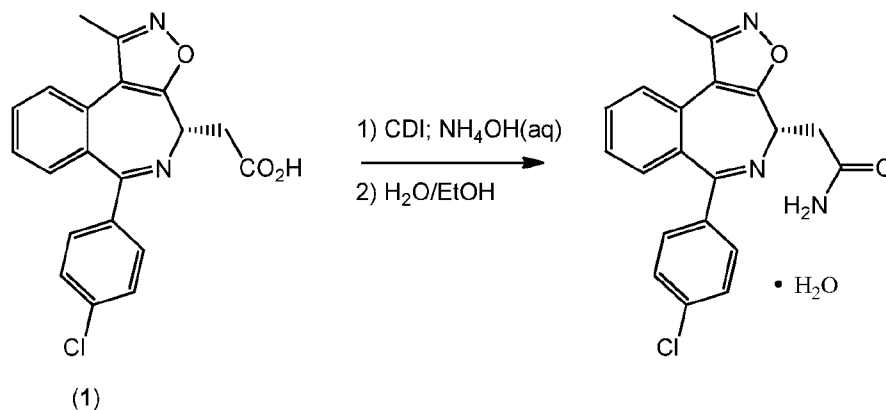
[0062] Differential Scanning Calorimetry was performed on a Mettler 822° on the sample “as is.” Sample were weighed in an aluminum pan, covered with a pierced lid, and then crimped and analyzed from 30 to 300 °C ramped at 10 °C/min.

[0063] Thermal Gravimetric Analysis was performed on a Mettler 851° SDTA/TGA on the sample “as is.” Samples were weighed in an alumina crucible and analyzed from 30 to 300 °C at 10 °C/min.

[0064] Nuclear Magnetic Resonance was performed on a 500 MHz Bruker AVANCE. Samples were dissolved in DMSO-d₆ with 0.05% tetramethylsilane for internal reference.

[0065] Determination of water content (Karl Fisher analysis) was performed as per USP <921>, method IC (coulometric titration). Samples were used as-is and hydranal-coulomat AD was used as the titrant.

Preparation of monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide



[0066] Carboxylic acid (1) was prepared from the procedures described in U.S. Patent Publication No. 2012/0157428. See e.g., Scheme 1, Step L of U.S. Patent Publication No. 2012/0157428. It should be noted that subsequent couplings following the procedures described in U.S. Patent Publication No. 2012/0157428 (e.g., the second step in Scheme 1, Step L) produced only amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. This amorphous material did not result in any observable diffraction using XRPD and was further characterized e.g., by gravimetric moisture sorption (Figure 6).

[0067] To produce crystalline material, a reactor was charged with 700 g of carboxylic acid (1) with 65.8 wt% ¹H NMR potency (460 g, 1.3 mol) in DCM (4.6 L). The batch was charged with carbonyldiimidazole (CDI, 264 g, 1.6 mol, 1.3 equiv) in four portions with the solids addition system. Over the course of the addition, the batch temperature was 15–18 °C. The batch was stirred for 1–2 hours at 20–25 °C when HPLC analysis indicated the starting material was <2%. The batch was cooled to 0–5 °C. The batch was charged with 28% aqueous ammonium hydroxide solution (432 mL, 6.5 mol, 5 equiv) by an addition funnel over 20 minutes while maintaining the temperature at 0–5 °C. The batch was stirred at 0–5 °C for 1 hour when HPLC analysis indicated the intermediate acyl-imidazole was <2%. The batch was warmed to 20–25 °C and DI water (2.3 L) was added. The batch was stirred vigorously for 15 minutes. The stirring was stopped and the phases were separated. The organic phase was washed with brine (2.3 L), dried (MgSO₄), treated with activated carbon

(46 g, Darco G-60), filtered, and washed with DCM (1.5 L). The combined filtrates and washes were concentrated to dryness by rotary evaporation. The residue was redissolved in absolute alcohol (2.3 L) and heated to 50–55 °C. The batch was charged with DI water (2.3 L) by addition funnel over 1 hour while maintaining the temperature 50–55 °C. The batch was cooled over a period of 2 hours and an oil, instead of solids, was observed to form. The batch was reheated to 50–55 °C and gradually cooled to 15–25 °C over a period of 12–16 hours. The batch was cooled to 0–5 °C and stirred for 1–2 hours. The batch was filtered and washed with a 1:1 mixture of DI water to absolute ethanol (230 mL).

[0068] The solids were dried under high vacuum at 40–45 °C overnight to afford monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide [320 g, 70% yield, 95.1% (AUC) by HPLC]. Robertson Microlit analyzed the palladium level to be 84 ppm. XRPD, NMR, TGA, DSC, and an optical micrograph are depicted in Figures 1-3 and 5. Karl Fisher analysis confirmed an average water content of 4.5 wt%. The listing of XRPD peaks shown in Figure 1 are provided in Table 1 below.

[0069] Table 1:

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
3.0336	1988.99	29.12462	52.73
3.1649	1327.33	27.91663	35.19
3.2884	1083.33	26.86863	28.72
3.4948	635.48	25.28248	16.85
3.9478	403.68	22.38208	10.70
4.0869	270.39	21.62063	7.17
4.7235	2628.10	18.70798	69.67
5.1531	236.70	17.14940	6.27
5.3536	198.61	16.50752	5.26
5.4960	267.67	16.08028	7.10
5.8237	242.60	15.17609	6.43
6.1496	241.07	14.37248	6.39
6.3895	216.18	13.83349	5.73
6.5144	215.41	13.56854	5.71
6.7353	204.99	13.12391	5.43
6.9871	215.41	12.65149	5.71
7.3109	227.93	12.09190	6.04
7.8162	302.06	11.31125	8.01
8.0948	734.50	10.92261	19.47
8.3685	197.39	10.56595	5.23
9.4026	3757.23	9.40614	99.60
9.6511	281.43	9.16446	7.46
9.8338	174.97	8.99467	4.64
11.4804	930.16	7.70797	24.66

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
12.2142	157.58	7.24649	4.18
12.9004	1039.92	6.86256	27.57
13.1776	982.45	6.71883	26.04
13.7115	667.90	6.45837	17.71
13.9053	1383.18	6.36881	36.67
14.0985	3561.75	6.28194	94.42
14.4812	248.41	6.11678	6.59
14.9529	432.73	5.92489	11.47
15.2740	230.77	5.80102	6.12
15.5561	531.22	5.69646	14.08
16.1928	268.83	5.47389	7.13
16.6155	277.70	5.33556	7.36
17.6687	283.77	5.01985	7.52
18.0818	1412.20	4.90606	37.44
18.4628	1032.14	4.80568	27.36
18.8178	3772.24	4.71581	100.00
19.2547	235.31	4.60979	6.24
19.6750	1469.98	4.51226	38.97
19.9576	201.73	4.44899	5.35
20.1690	316.47	4.40283	8.39
20.4059	638.01	4.35224	16.91
21.1124	291.75	4.20818	7.73
21.4065	1204.64	4.15103	31.93
21.9339	862.26	4.05239	22.86
22.2025	1399.21	4.00397	37.09
22.7872	436.98	3.90253	11.58
23.0528	893.69	3.85817	23.69
23.3225	749.60	3.81417	19.87
23.6892	412.87	3.75595	10.94
24.2339	1031.93	3.67274	27.36
25.1459	1568.45	3.54156	41.58
26.0516	1213.60	3.42046	32.17
26.4951	606.60	3.36420	16.08
26.8154	558.47	3.32474	14.80
27.3459	360.81	3.26144	9.56
27.8110	411.96	3.20795	10.92
28.5558	302.69	3.12594	8.02
28.7720	149.82	3.10294	3.97
29.0442	406.42	3.07448	10.77
30.0560	307.13	2.97325	8.14
30.9196	206.76	2.89215	5.48
31.6090	444.00	2.83063	11.77
32.2544	62.89	2.77544	1.67
32.8271	163.83	2.72832	4.34
33.1645	177.25	2.70133	4.70
33.7924	382.04	2.65256	10.13
34.6255	229.21	2.59062	6.08

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
36.2737	143.43	2.47660	3.80
36.9392	48.33	2.43350	1.28
37.4803	54.57	2.39960	1.45
38.1235	94.49	2.36058	2.50
38.6912	84.88	2.32725	2.25
39.6424	51.55	2.27357	1.37
40.1581	73.63	2.24556	1.95
41.1015	59.40	2.19617	1.57
42.0541	24.56	2.14860	0.65
43.0617	132.72	2.10063	3.52
44.4472	57.70	2.03663	1.53

[0070] GMP scale up of monohydrate crystalline Form A was performed as follows. 3955 g of crude 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, was dissolved in prefiltered EtOH (15 L, 5.5 vol) at room temperature and transferred to a 100 L, jacketed reactor. The batch temperature was set to 55 ± 5 °C and purified water (15L, 5.5 vol) was added while maintaining the batch temperature at 55 ± 5 °C over a period of 42 min. Batch temperature was set to 45 ± 5 °C and monohydrate Form A Seed Crystals (6.1 g) were added. The batch was cooled to 20 ± 5 °C over a period of 5 h and further cooled to 0 ± 5 °C over a period of 55 min. Stirring continued for an additional 1 h at 0 ± 5 °C. The resulting solids were filtered and the filter cake was washed with a 1:1 room temperature mixture of prefiltered ethanol (1.5 L) and purified water (1.5 L). The solids were transferred to glass trays and dried in a vacuum oven at 45 ± 5 °C with a nitrogen bleed to provide 2.15 kg (75%) of monohydrate crystalline Form A as an off-white solid. XRPD, DSC, and TGA are depicted in Figures 13-15. Karl Fisher analysis confirmed a water content of 4.3 wt%. The listing of XRPD peaks shown in Figure 10 are provided in Table 2 below.

[0071] Table 2

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
3.4080	740.11	25.92592	54.27
3.8112	343.38	23.18414	25.18
3.9533	413.37	22.35104	30.31
4.2321	235.42	20.87945	17.26
4.4246	449.77	19.97141	32.98
4.7265	1019.48	18.69635	74.76
5.4063	238.73	16.34693	17.51
5.7155	226.66	15.46312	16.62
6.0881	196.79	14.51766	14.43
6.5332	166.88	13.52957	12.24
7.0002	254.60	12.62787	18.67
7.2643	188.77	12.16931	13.84

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
7.6543	183.76	11.55018	13.47
8.1056	527.23	10.90808	38.66
9.0552	260.59	9.76617	19.11
9.4205	1036.06	9.38832	75.97
10.2693	190.66	8.61415	13.98
10.7274	115.42	8.24730	8.46
10.9628	145.29	8.07073	10.65
11.4960	574.76	7.69754	42.15
11.9277	131.43	7.41995	9.64
12.2366	234.28	7.23329	17.18
12.9118	978.84	6.85650	71.78
13.1919	1003.96	6.71154	73.62
13.6997	640.80	6.46391	46.99
13.9273	1276.77	6.35878	93.62
14.0969	1264.85	6.28265	92.75
14.5209	235.92	6.10015	17.30
14.9684	476.37	5.91879	34.93
15.5806	246.37	5.68756	18.07
16.2278	218.55	5.46216	16.03
16.6266	195.39	5.33205	14.33
17.3982	123.37	5.09725	9.05
17.6658	302.19	5.02064	22.16
18.0877	1305.56	4.90447	95.73
18.4827	882.00	4.80054	64.67
18.7987	1285.08	4.72056	94.23
19.2100	257.04	4.62041	18.85
19.7033	1073.72	4.50582	78.73
20.2147	321.21	4.39299	23.55
20.4209	380.63	4.34909	27.91
21.1031	150.77	4.21001	11.06
21.4152	941.01	4.14935	69.00
21.9650	602.58	4.04671	44.18
22.1686	562.27	4.01001	41.23
22.8147	320.56	3.89789	23.51
23.0759	644.48	3.85436	47.26
23.3517	549.90	3.80946	40.32
23.7273	277.30	3.75000	20.33
24.2598	1100.96	3.66887	80.73
25.1699	1363.76	3.53825	100.00
26.0748	810.12	3.41747	59.40
26.5288	465.03	3.36001	34.10
26.8295	329.14	3.32303	24.13
27.3416	308.65	3.26194	22.63
27.8286	280.09	3.20595	20.54
28.5953	220.56	3.12172	16.17
28.8334	196.35	3.09648	14.40
29.0462	278.36	3.07173	20.41

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
29.1504	283.60	3.06352	20.80
30.0960	306.43	2.96939	22.47
30.9361	102.55	2.89064	7.52
31.5911	306.56	2.83219	22.48
32.8056	115.64	2.73006	8.48
33.1879	97.15	2.69948	7.12
33.7004	221.32	2.65959	16.23
34.6463	144.49	2.58912	10.60
35.6301	23.03	2.51985	1.69
36.2831	67.12	2.47598	4.92
36.8903	50.77	2.43661	3.72
37.4872	45.00	2.39918	3.30
39.7062	48.73	2.27007	3.57
40.0574	39.85	2.25097	2.92
40.8783	44.10	2.20764	3.23
41.2199	21.83	2.19014	1.60
43.0651	70.94	2.10047	5.20
44.4896	35.20	20.3479	2.58

[0072] Examples of formulations comprising the crystalline forms described herein are as follows.

2 mg capsules

Ingredients	Function	Weight Composition (%, w/w)	Weight per Unit Dosage (mg)
Monohydrate Crystalline Form A	API	1.25	2.0
Microcrystalline Cellulose (Avicel PH-101)	Filler	97.75	156.4
Magnesium Stearate (Vegetable Grade, Hyqual)	Lubricant	1.00	1.6
HPMC capsule, size 2, white opaque (Vcaps Plus)	Capsule shell	NA	1 each
Total		100.00	160.0

10 mg capsules

Ingredients	Function	Weight Composition (%, w/w)	Weight per Unit Dosage (mg)
Monohydrate Cystalline Form A	API	3.60	10.0
Microcrystalline Cellulose (Avicel PH-101)	Filler	95.00	267.2
Magnesium Stearate (Vegetable Grade, Hyqual)	Lubricant	1.00	2.8
HPMC capsule, size 0, Swedish Orange (Quali Vcaps)	Capsule shell	NA	1 each
Total		100.00	280.0

25 mg capsules

Ingredients	Function	Weight Composition (%, w/w)	Weight per Unit Dosage (mg)
Monohydrate Cystalline Form A	API	8.93	25.0
Microcrystalline Cellulose (Avicel PH-101)	Filler	90.57	253.6
Magnesium Stearate (Vegetable Grade, Hyqual)	Lubricant	0.50	1.4
HPMC capsule, size 0, Rich yellow Opaque (Vcap Plus)	Capsule shell	NA	1 each
Total		100.00	280.0

[0073] Micronized Forms

Ingredient	Function	weight composition (w/w %)	weight (mg) per unit dosage (25 mg tablet)	weight (mg) per unit dosage (50 mg tablet)	weight (mg) per unit dosage (100 mg tablet)
Intragranular					
Micronized Monohydrate Form A	API	12.5	25.0	50.0	100.0
Microcrystalline cellulose	Diluent / filler	30.0	60.0	120.0	240.0
Lactose monohydrate	Diluent / filler	45.0	90.0	180.0	360.0
Croscarmellose sodium	Disintegrant	2.0	4.0	8.0	16.0
Hydroxypropyl cellulose	Binder	3.5	7.0	14.0	28.0
Sodium lauryl sulfate	surfactant	3.0	6.0	12.0	24.0
Purified water	Granulating liquid	qs	qs	qs	qs
Extragranular					
Croscarmellose sodium	Disintegrant	2.0	4.0	8.0	16.0
Colloidal silicon dioxide	Glidant	1.0	2.0	4.0	8.0
Magnesium stearate	Lubricant	1.0	2.0	4.0	8.0
Total intragranular		100.0	200.0	400.0	800.0

Certain Advantages of monohydrate Form A over amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

Relative Humidity Stability

[0074] As shown by the gravimetric moisture sorption curve for monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in Figure 4, the stability of the monohydrate stoichiometry (water content) remains effectively constant at the monohydrate state (at approximately 5%, theoretical content of 4.6%) over a relative humidity range of 5 to 95%. This level of stability is rare for many pharmaceutical compounds, and particularly for hydrated forms since most are typically stable only at lower threshold values. Typically, one would expect to see stability of a monohydrate stoichiometry over a more limited range, e.g., between 30 to 70%. At relative humidity levels below 30% a compound would still retain water, but the stoichiometric ratio would be less than that of a

true monohydrate. Likewise, at high relative humidity, the stoichiometric ratio of water to compound would exceed that of a monohydrate. As evidenced by Figure 4, this was not observed with monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. Rather, the stoichiometric ratio of water to monohydrate remained stable throughout the relative humidity range of 5 to 95%.

[0075] This unanticipated observed stability of the monohydrate Form A over such a broad humidity range would be advantageous in pharmaceutical formulations (e.g., tablets and capsules) since the water content of monohydrate Form A should have minimal effect on the water content of excipients and, likewise, the water content of the excipients would have minimal impact on the monohydrate Form A water content.

[0076] Unlike the moisture vapor profile of the disclosed monohydrate Form A, the water content of microcrystalline cellulose changes from 4 wt% at 20% relative humidity to approximately 18 wt% at 90% relative humidity. In a pharmaceutical formulation blend comprising an API with an excipient like, e.g., microcrystalline cellulose, or in a compressed tablet, the water content of the API and the excipients will equilibrate. Since the water content of the disclosed monohydrate Form A remains very consistent from 5 to 95% RH one achieves the unexpected advantage of not having to be concerned with the excipient(s) (e.g., microcrystalline cellulose) giving up water to the API or vice versa, which could lead to changes in API stability or to changes in friability or disintegration properties upon storage.

[0077] In contrast, Figure 6 shows a gravimetric moisture sorption curve for amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, where the water content of the amorphous form was found to increase from 0 to approximately 95% relative humidity. Thus, and in contrast to the disclosed monohydrate Form A, amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide does not exhibit an effectively constant stoichiometric ratios of water over a broad relative humidity range and, as such, the aforementioned concerns and changes may be realized.

Relative Stability

[0078] In deionized water, the monohydrate Form A was found to be stable with a solubility of 4.5 $\mu\text{m}/\text{mL}$. However, upon slurry of the amorphous form in deionized water for 24 hr at ambient temperature conversion to monohydrate Form A was observed.

Pharmacokinetic comparison of monohydrate Form A and amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide.

[0079] For many active pharmaceutical ingredients it has been shown that different forms have different pharmacokinetic profiles. Compared to amorphous solid, crystalline solids have often lower oral bioavailability (Qiu Y., J Pharm Sci, 2004, 93:563). Data below demonstrates that monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has favorable pharmacokinetic profile in rats and dogs and are similar to what was observed with the amorphous solid. Results demonstrate that Form A is suitable for use in human for treatment of disease.

[0080] Monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide was discovered to have the following favorable and unexpected properties: similar pharmacokinetic profile to the amorphous solid when administered as a suspension in Methylcellulose; small inter-individual variability; acceptable dose exposure proportionality; and favorable pharmacokinetic profile when administered as powder in a capsule.

Pharmacokinetic of monohydrate Form A and amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in rat

[0081] Male Sprague Dawley rats were dosed at 60 mg/Kg orally once using a suspension of amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in 0.5% Methylcellulose. Individual plasma concentrations are reported in Table 3 and calculated pharmacokinetic parameters are reported in Table 4.

[0082] Table 3: Plasma concentration of amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 60 mg/Kg.

Time (h)	R 2007	R 2008	R 2009	R 2010	R 2011	R 2012	Mean
1				12700	13800	8650	11700
2	14900	12100	8830				11900
4				8410	11800	9370	9860
8	6550	6450	6310				6440
24				BQL	BQL	BQL	BQL

[0083] Table 4: Calculated pharmacokinetic parameters of amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 60 mg/Kg.

C _{max} (ng/mL)	11900
T _{max} (h)	2.0
AUC _{0-last} (ng·h/mL)	123000

[0084] Male Sprague Dawley rats were dosed at 60 mg /Kg orally once using a suspension of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in 0.5% Methylcellulose. Individual plasma concentrations are reported in Table 5 and calculated pharmacokinetic parameters are reported in Table 6.

[0085] Table 5: Plasma concentration of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 60 mg/Kg.

Time (h)	R7	R8	R9	R10	R11	R12	Mean	SD
0.0830	183	407	512	158	391	172	304	± 152
0.250	1830	2770	2670	2150	2050	1420	2148	± 510
0.500	3610	5250	3790	4120	4050	3550	4062	± 625
1.00	5290	6110	6840	5440	4740	4770	5532	± 815
2.00	8220	7490	6700	8330	6850	5590	7197	± 1036
4.00	7740	4850	5160	8350	5690	4650	6073	± 1579
8.00	3050	805	1220	1960	2320	1200	1759	± 841
24.0	BQL	BQL	BQL	1.04	BQL	BQL	ND	± --

[0086] Table 6: Calculated pharmacokinetic parameters of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 60 mg/Kg.

C _{max} (ng/mL)	7197
T _{max} (h)	2.0
AUC _{0-last} (ng·h/mL)	52800

[0087] Based on those two studies in male Sprague Dawley rats at 60 mg/Kg, monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide has a similar pharmacokinetic profile to the amorphous form when administered as a suspension in Methylcellulose. This is a favorable and unexpected property of the monohydrate crystalline form.

Dose escalation with form A in male Sprague Dawley rats

[0088] A suspension of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide suspended in 0.5% Methylcellulose was dosed to Male Sprague Dawley rats at 10 mg/Kg and 60 mg/Kg orally. Individual plasma concentrations for the 10 mg/Kg dose and the 60 mg/Kg dose are reported on Table 7 and Table 5 respectively. Respective pharmacokinetic parameters and pharmacokinetic profiles are reported in Table 8 and in Figure 7.

[0089] Table 7: Plasma concentration of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 10 mg/Kg.

Time (h)	R1	R2	R3	R4	R5	R6	PO1	SD
0.0830	51.3	182	89.2	191	166	31.5	119 ±	70.0
0.250	799	1240	809	1060	767	769	907 ±	197
0.500	1420	1410	1420	2000	1440	1600	1548 ±	233
1.00	1940	1620	1510	2300	1790	1600	1793 ±	292
2.00	1400	1320	1420	1650	950	1000	1290 ±	268
4.00	611	349	569	544	166	255	416 ±	185
8.00	56.3	18.1	32.4	13.6	2.93	18.2	23.6 ±	18.6
24.0	BQL	BQL	BQL	BQL	BQL	BQL	ND ±	--

[0090] Table 8: Calculated pharmacokinetic parameters of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male Sprague Dawley rats at 10 and 60 mg/Kg.

Doses (mg/Kg)	10	60
C _{max} (ng/mL)	1793	7197
T _{max} (h)	1.0	2.0
AUC _{0-last} (ng·h/mL)	5500	52800

[0091] When monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is administered orally as a suspension in Methylcellulose in male Sprague Dawley rats, both the C_{max} and the AUC increase slightly more than proportionally with the dose as the dose increases from 10 to 60 mg/Kg. (See e.g., Figure 7). Low inter-individual differences are also observed at both doses. These are favorable and unexpected properties of the monohydrate crystalline Form A solid.

Pharmacokinetic of monohydrate Form A and amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide in dog

[0092] Amorphous and monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide were dosed orally in dogs at 2 mg/Kg. Both forms (amorphous and monohydrate Form A) were suspended in Methylcellulose (0.4 mg/mL in 0.5 % MC). The objective was to compare the pharmacokinetic profiles of both forms in dogs using a crossover study design in which the same dogs were dosed sequentially with amorphous and monohydrate crystalline Form A with a washout period in between. Results are summarized below.

[0093] Table 9: Plasma concentration and pharmacokinetic parameters of amorphous form of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male beagle dog at 2mg/Kg.

Time (h)	D101	D102	D103	D104	D105	D106	Mean	SD	CV(%)	
0	BQL	BQL	BQL	BQL	BQL	BQL	NC	±	NC	NC
0.25	85.7	90.1	313	133	126	381	188	±	126	67.1
0.5	482	390	589	444	341	581	471	±	100	21.3
1	609	646	609	672	705	706	658	±	43.9	6.68
2	596	444	621	555	623	621	577	±	70.0	12.1
4	455	451	681	537	487	558	528	±	86.4	16.4
6	339	230	308	308	263	288	289	±	38.4	13.3
8	240	214	255	241	172	268	232	±	34.3	14.8
12	157	134	173	154	114	184	153	±	25.5	16.7
24	61.6	49.0	87.8	75.8	33.8	76.2	64.0	±	20.0	31.2
C_{max} (ng/mL)	609	646	681	672	705	706	670	±	37.3	5.56
T_{max} (h)	1.00	1.00	4.00	1.00	1.00	1.00	1.50	±	1.22	81.6
$T_{1/2}$ (h)	8.31	7.86	10.17	9.21	6.82	9.17	8.59	±	1.18	13.7
AUC_{0-last} (ng·h/mL)	5370	4560	6220	5540	4610	6060	5393	±	701	13.0
AUC_{0-inf} (ng·h/mL)	6110	5120	7510	6550	4950	7070	6218	±	1033	16.6
MRT_{0-last} (h)	7.59	7.45	7.73	7.73	6.48	7.69	7.45	±	0.48	6.51
MRT_{0-inf} (h)	11.02	10.48	13.04	12.28	8.32	11.90	11.17	±	1.67	14.9

[0094] Table 10: Plasma concentration and pharmacokinetic parameters of monohydrate Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide following single oral dose to male beagle dog at 2mg/Kg.

Time (h)	D101	D102	D103	D104	D105	D106	Mean	SD	CV(%)
0	BQL	BQL	BQL	BQL	BQL	BQL	NC	±	NC
0.25	126	166	147	49.2	4.96	108	100	±	61.5
0.5	333	296	410	292	257	390	330	±	59.9
1	542	465	615	419	522	569	522	±	70.9
2	483	482	558	459	549	541	512	±	42.1
4	414	359	506	332	546	451	435	±	83.0
6	273	257	314	226	321	275	278	±	35.6
8	209	171	240	165	253	248	214	±	39.1
12	140	113	190	114	161	188	151	±	34.4
24	56.3	42.9	95.0	61.0	69.0	78.1	67.1	±	18.1
No.points of t _{1/2}	3	3	3	3	4	3	--	±	--
C _{max} (ng/mL)	542	482	615	459	549	569	536	±	57.2
T _{max} (h)	1.00	2.00	1.00	2.00	2.00	1.00	1.50	±	0.55
T _{1/2} (h)	8.60	8.14	11.97	11.58	8.31	9.57	9.70	±	1.69
AUC _{0-last} (ng·h/mL)	4650	4040	5850	3960	5390	5460	4892	±	793
AUC _{0-inf} (ng·h/mL)	5350	4540	7490	4980	6220	6540	5853	±	1098
MRT _{0-last} (h)	7.74	7.34	8.38	8.01	7.93	8.32	7.95	±	0.39
MRT _{0-inf} (h)	11.49	10.49	15.59	14.70	11.66	13.18	12.85	±	1.99

[0095] Both the amorphous solid and the monohydrate crystalline Form A show similar pharmacokinetic profiles and low inter-individual variability. These are favorable and unexpected properties of the monohydrate crystalline Form A.

[0096] While have described a number of embodiments of this, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this disclosure. Therefore, it will be appreciated that the scope of this disclosure is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[0097] Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

We Claim:

1. Crystalline monohydrate Form A of 24(4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, wherein the crystalline form is characterized by at least three x-ray powder diffraction peaks at 2θ angles selected from 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° .
2. The crystalline Form A of Claim 1, wherein the crystalline form is characterized by at least four x-ray powder diffraction peaks at 2θ angles selected from 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° .
3. The crystalline Form A of Claim 1 or 2, wherein the crystalline form is characterized by at least five x-ray powder diffraction peaks at 2θ angles selected from 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° .
4. The crystalline Form A of any one of Claims 1 to 3, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2θ angles 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° .
5. The crystalline Form A of any one of Claims 1 to 4, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2θ angles 4.73° , 9.42° , 12.91° , 18.09° , 18.48° , 18.80° , 19.70° , 21.42° , and 25.17° .
6. The crystalline Form A of any one of Claims 1 to 5, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2θ angles 4.73° , 8.11° , 9.42° , 12.91° , 14.10° , 14.97° , 18.09° , 18.48° , 18.80° , 19.70° , 21.42° , and 25.17° , 26.07° , and 26.53° .
7. A pharmaceutical composition comprising the crystalline form of any one of Claims 1-6; and a pharmaceutically acceptable carrier or diluent.

8. A process for preparing monohydrate crystalline Form A of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, the process comprising:

forming the monohydrate crystalline Form A from a solution comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and water; or from a mixture comprising amorphous 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, and a combination of water and organic solvent, wherein the crystalline form is characterized by at least three x-ray powder diffraction peaks at 2θ angles selected from 4.73° , 18.09° , 18.48° , 18.80° , 19.70° , and 25.17° .

9. The process of Claim 8, wherein the combination of water and organic solvent is selected from ethanol/water, isopropanol/water, tetrahydrofuran/water, acetone/water, methanol/water, and acetonitrile/water.

10. The process of Claim 8 or 9, wherein the combination of water and organic solvent is ethanol/water.

11. The process of any one of Claims 8 to 10, wherein the combination of water and organic solvent is a 60:40 mixture of ethanol/water.

12. Use of the crystalline form of any one of Claims 1 to 6, for treating a bromodomain-containing protein-mediated disorder in a patient in need thereof.

13. Use of the crystalline form of any one of Claims 1 to 6, for the preparation of a medicament for treating a bromodomain-containing protein-mediated disorder in a patient in need thereof.

14. The use of claim 12 or 13, wherein the disorder is a proliferative disorder, an inflammatory disease, sepsis, an autoimmune disease, or a viral infection.

1/12

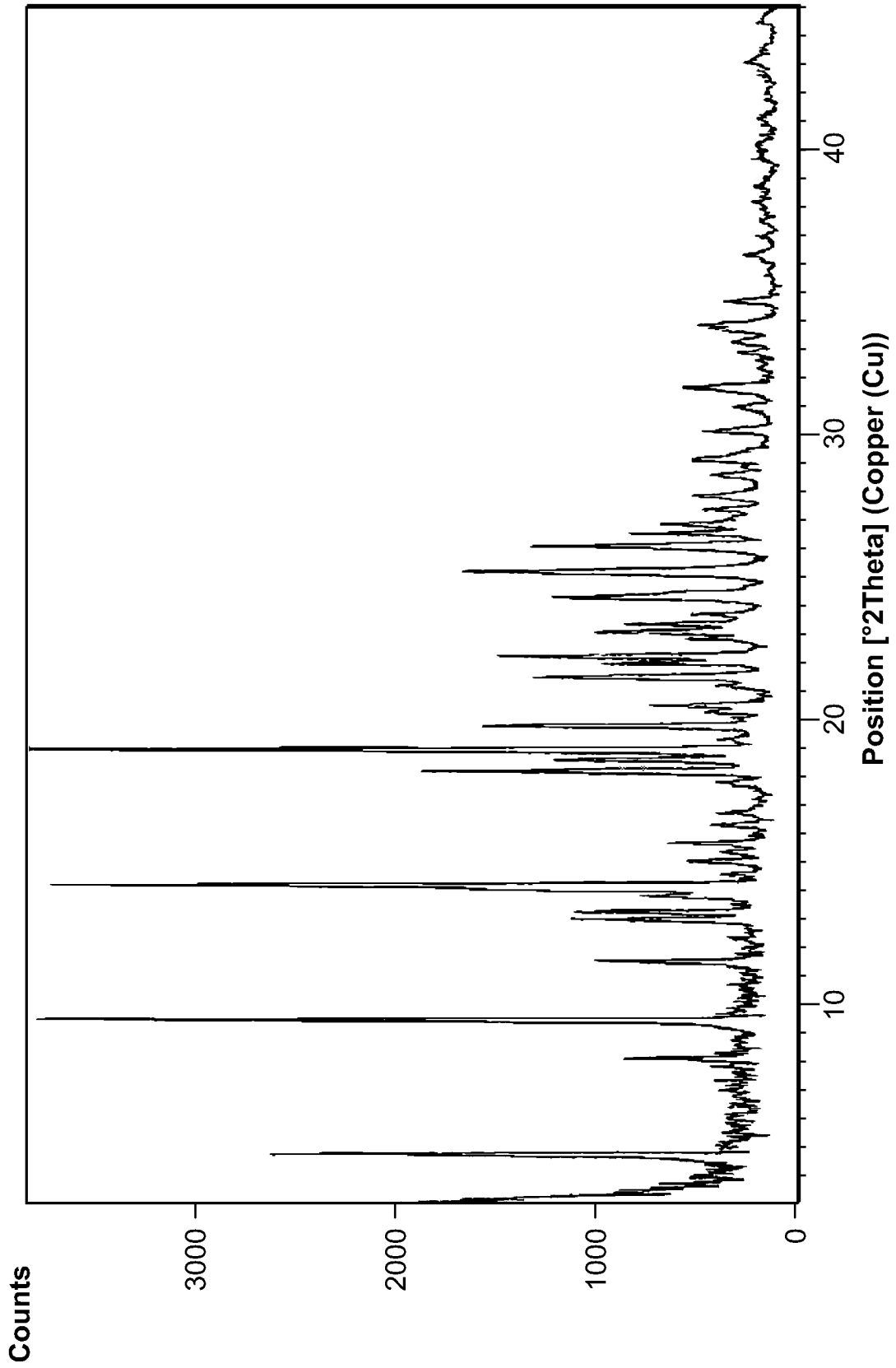


FIG. 1

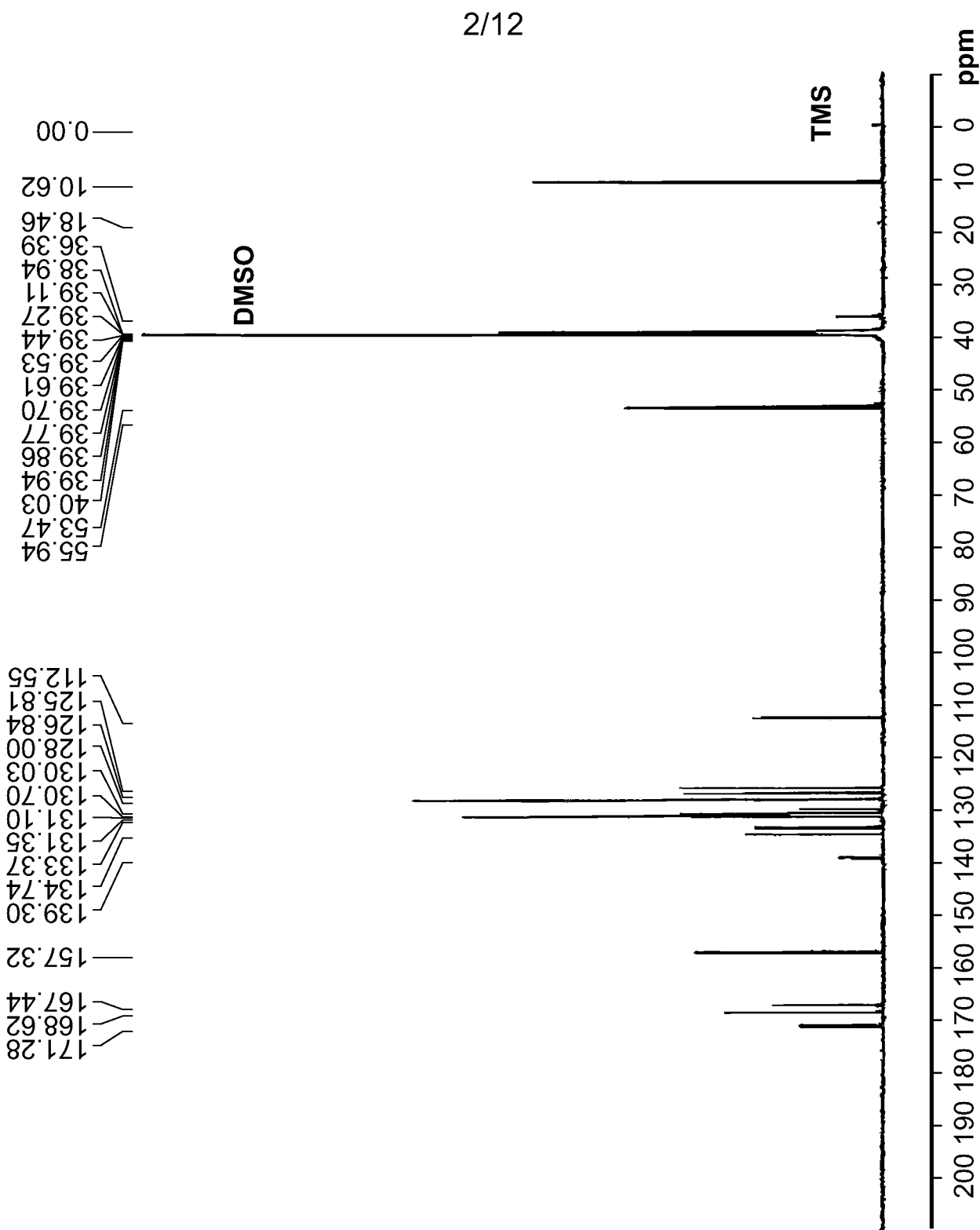


FIG. 2

3/12

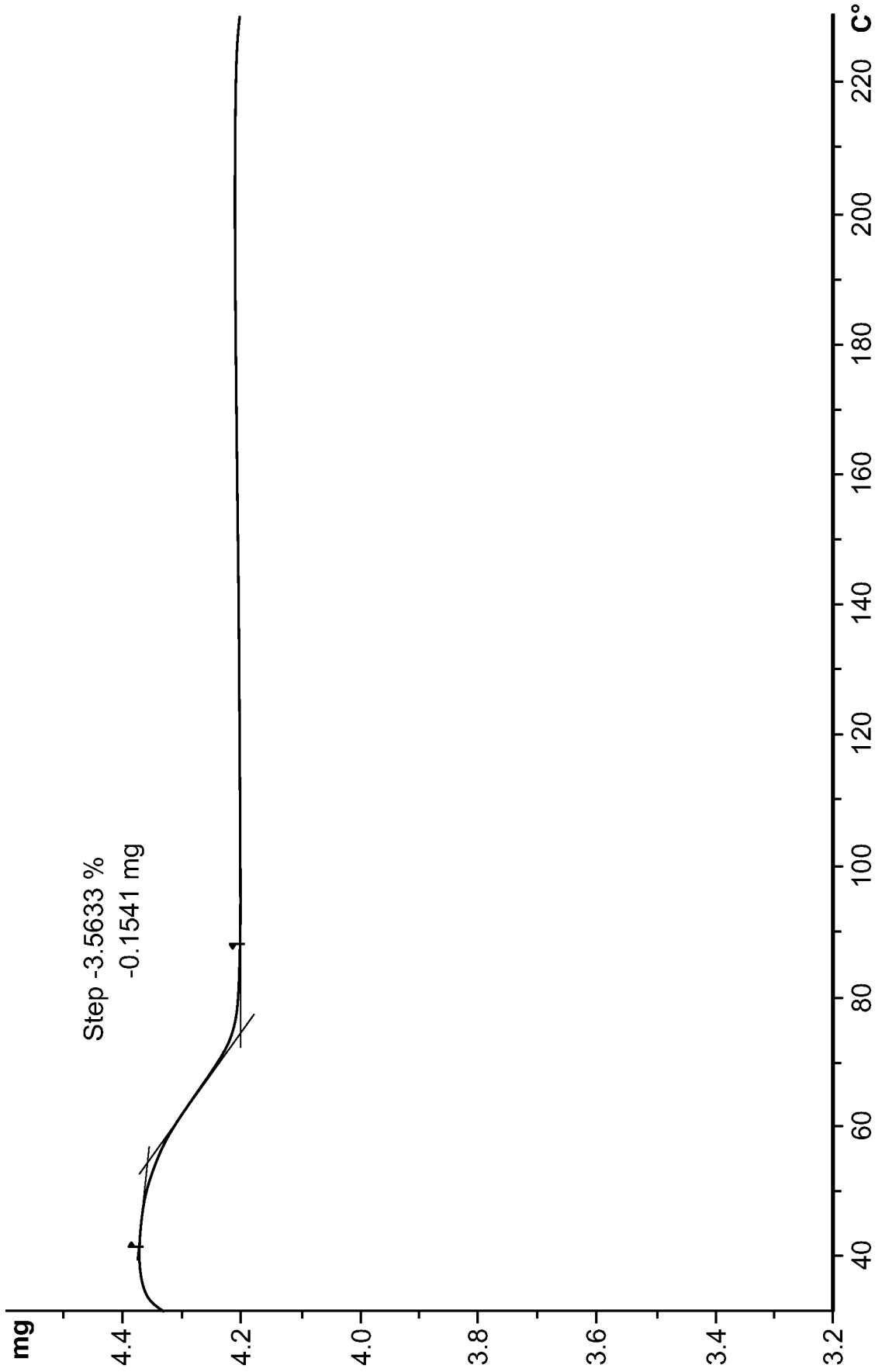


FIG. 3

4/12

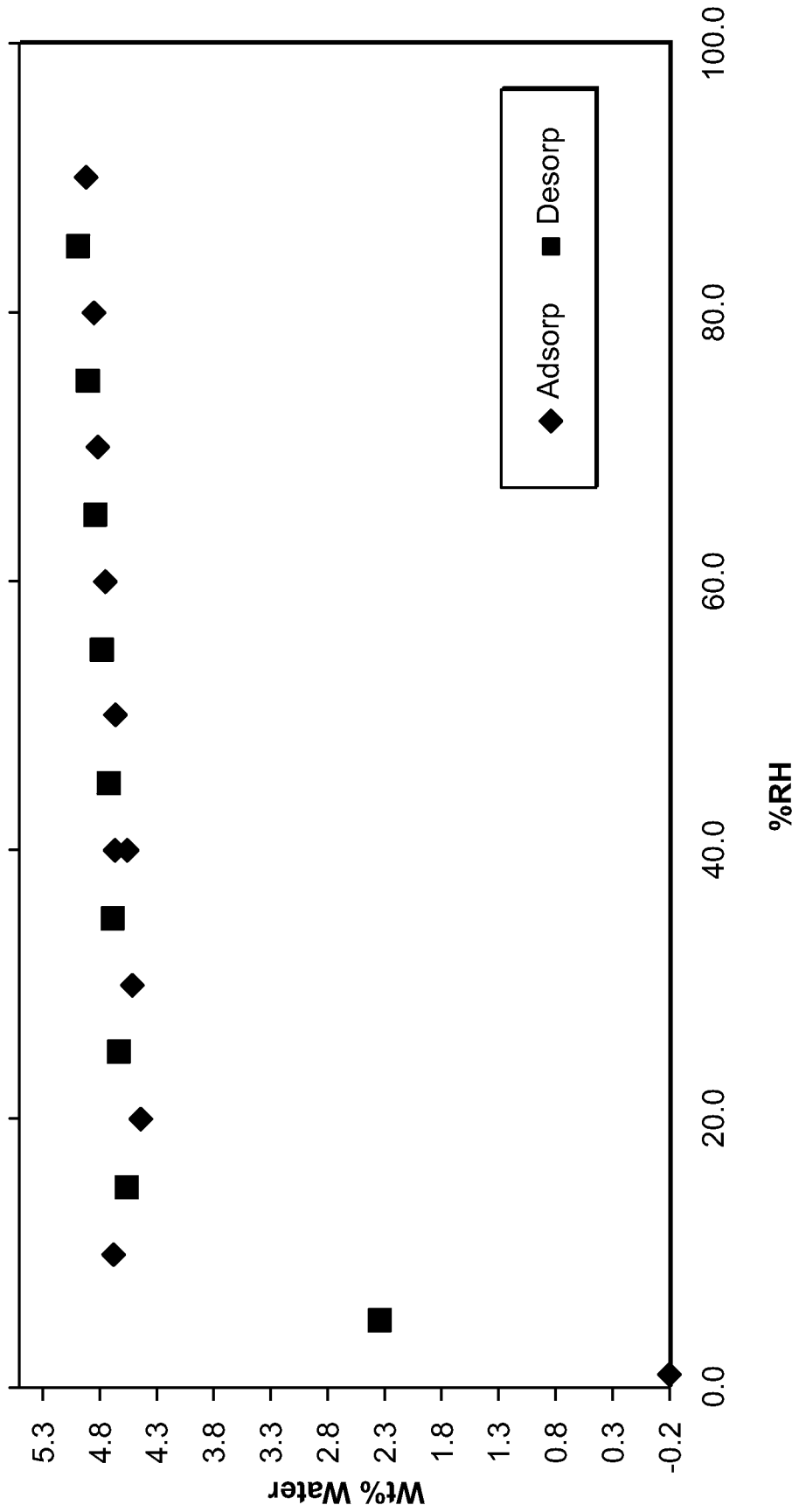


FIG. 4

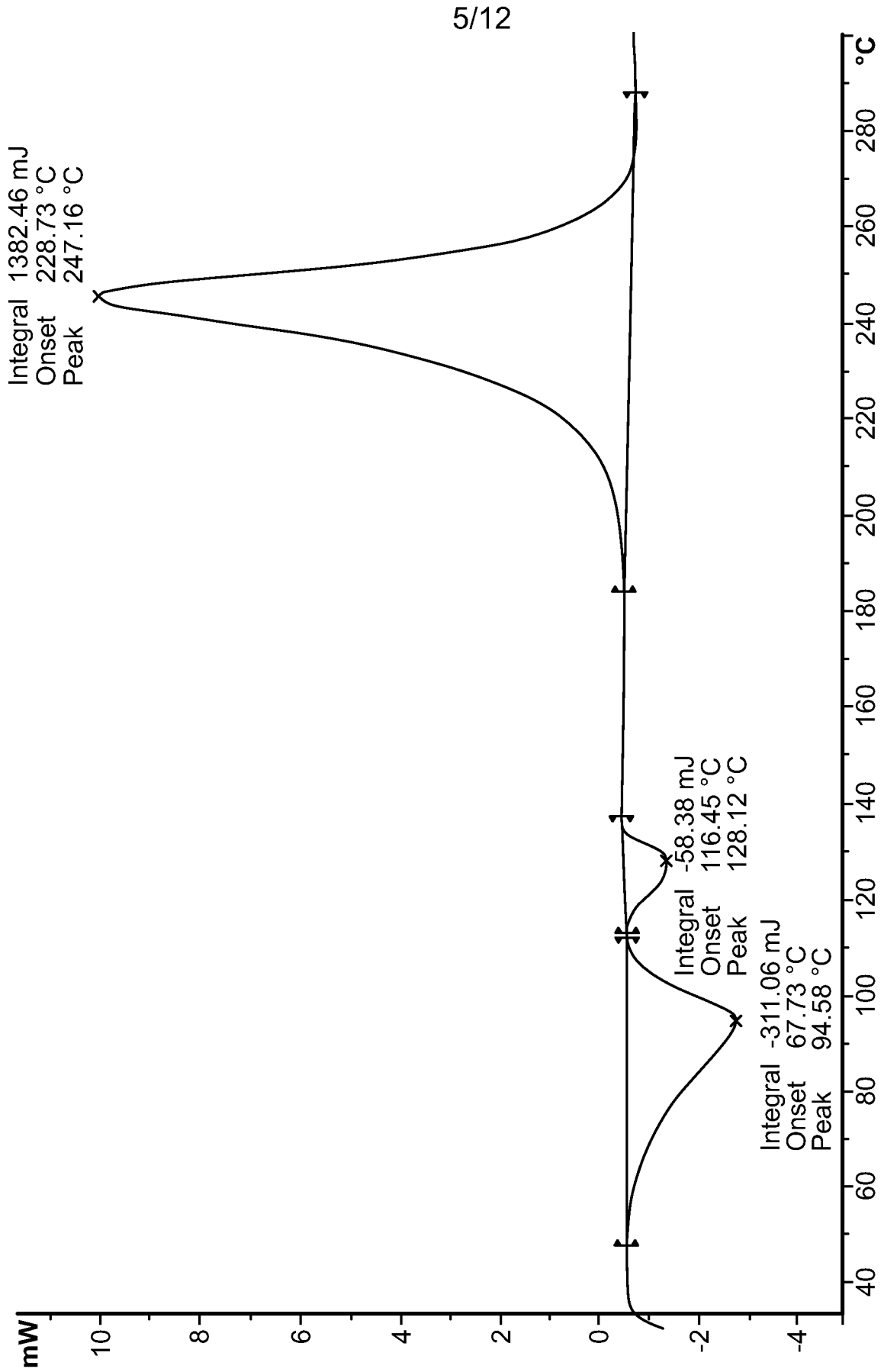


FIG. 5

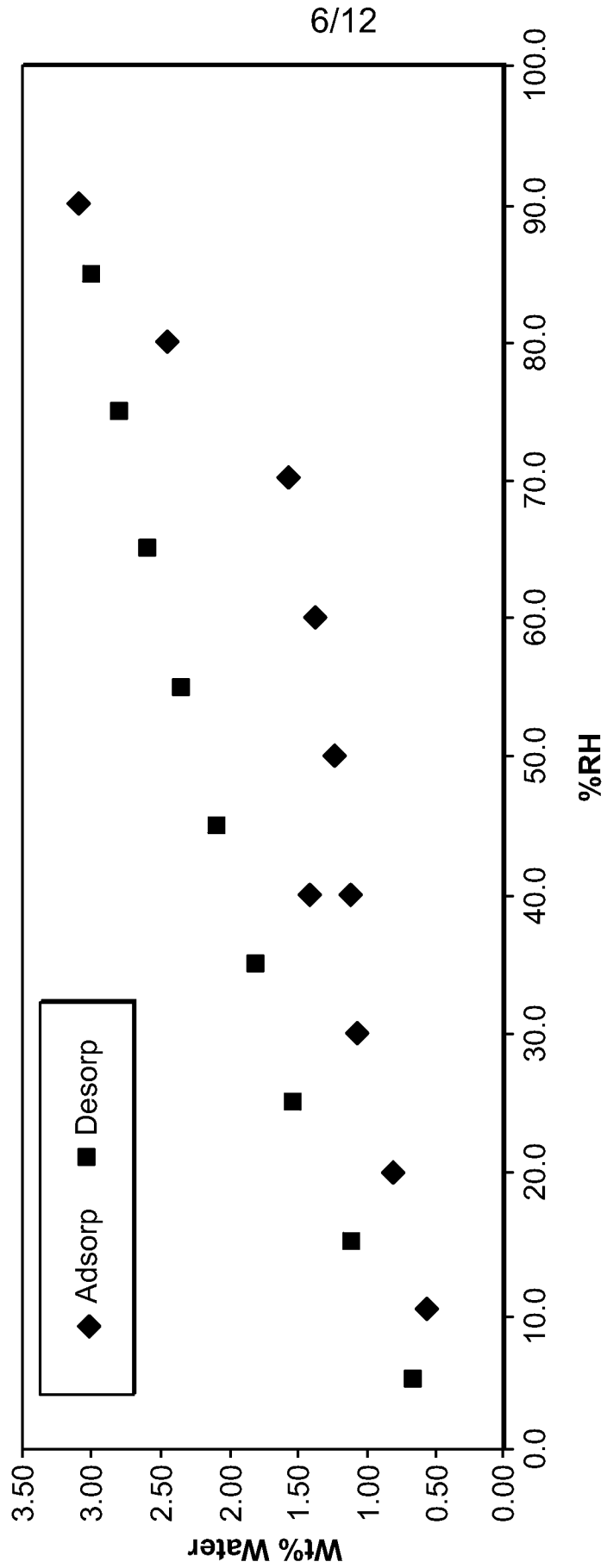


FIG. 6

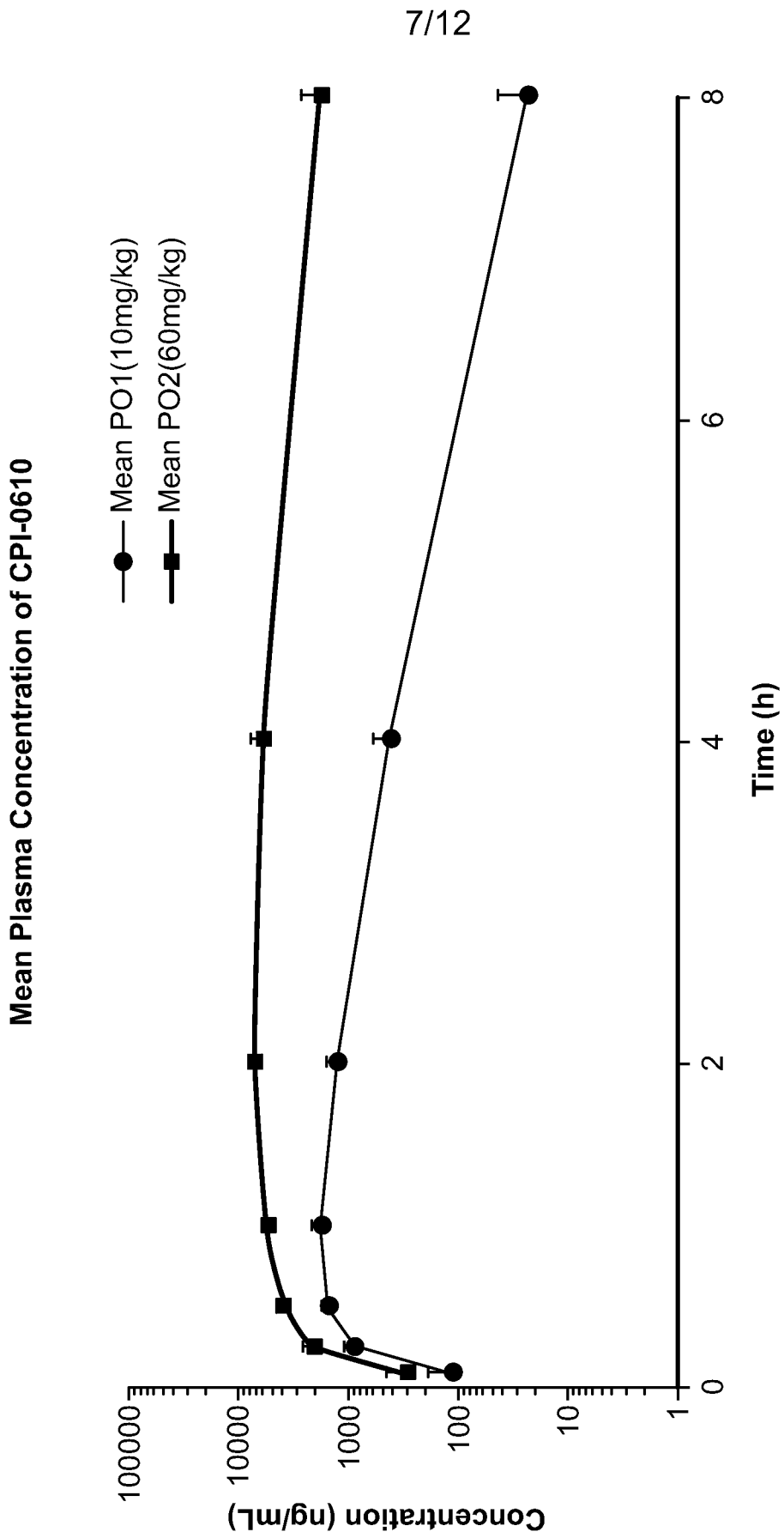


FIG. 7

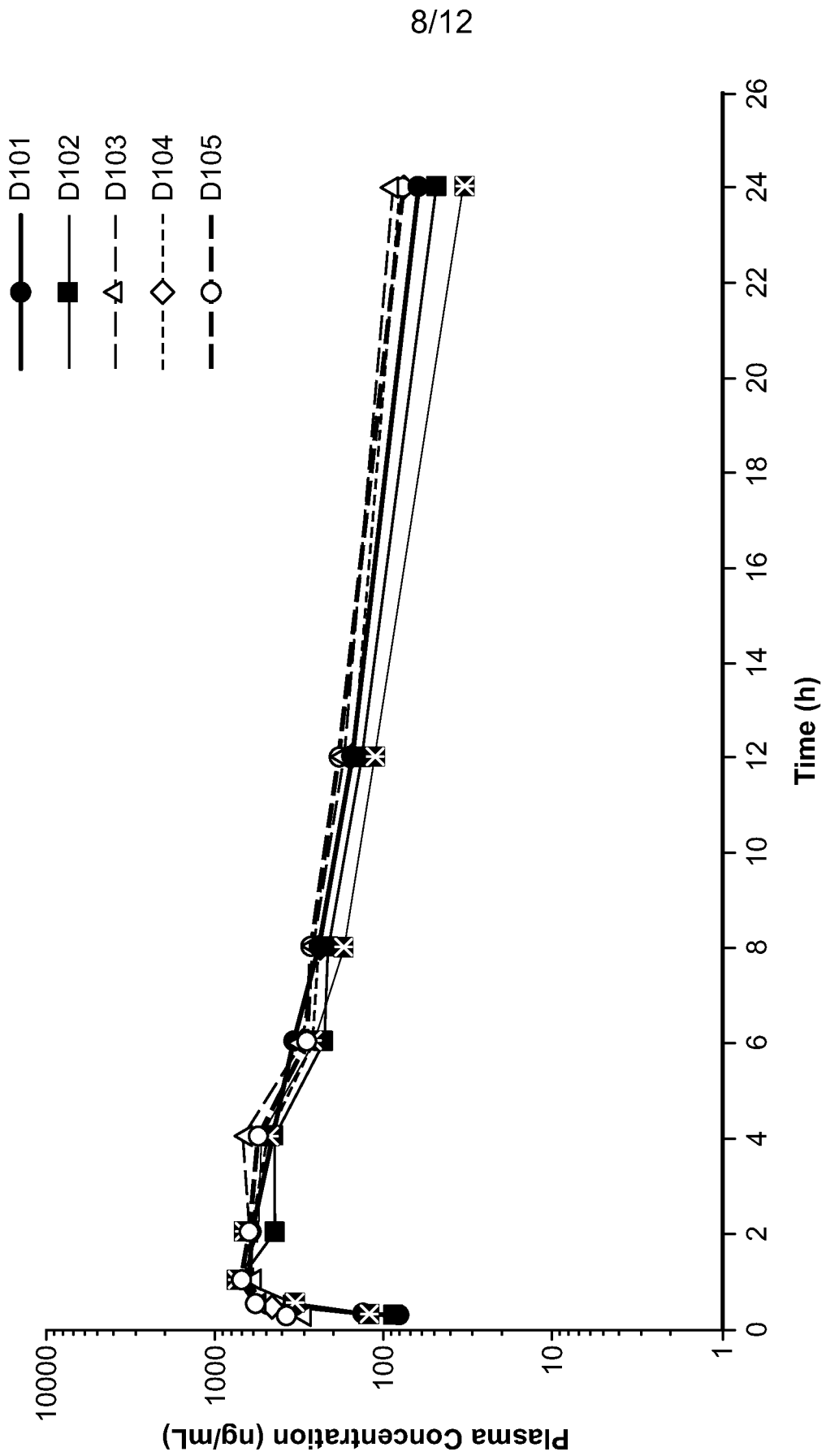


FIG. 8

9/12

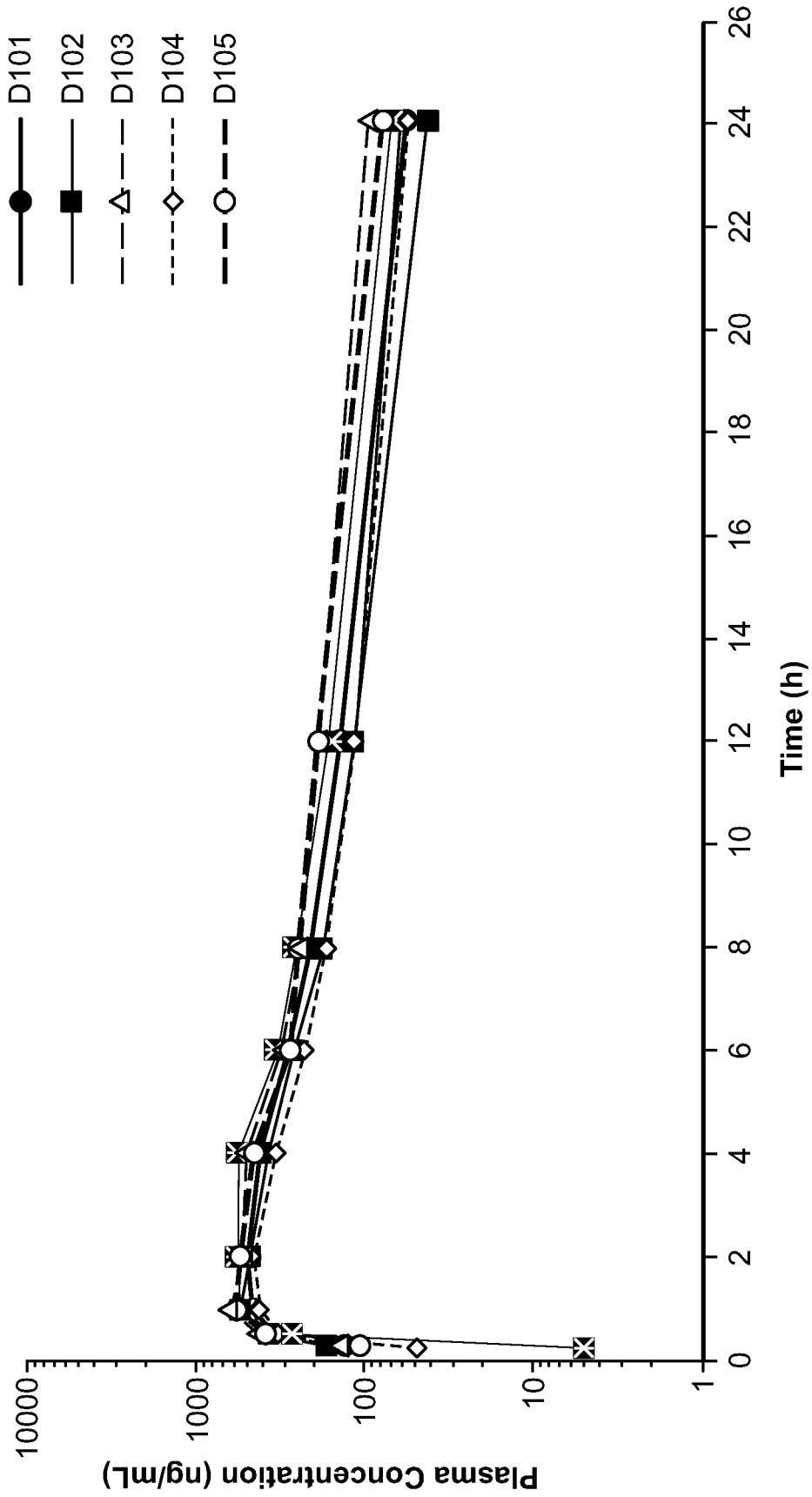


FIG. 9

10/12

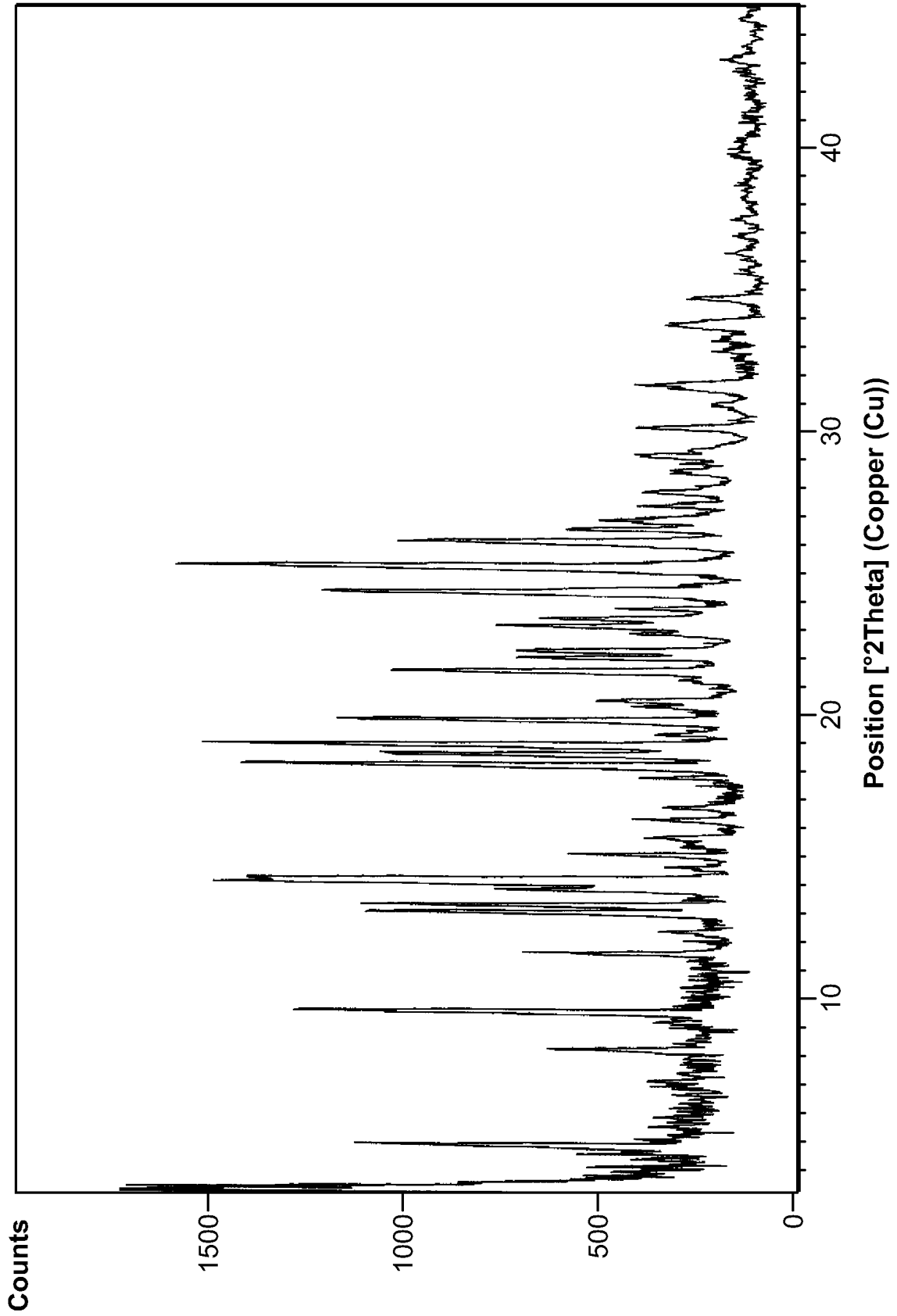


FIG. 10

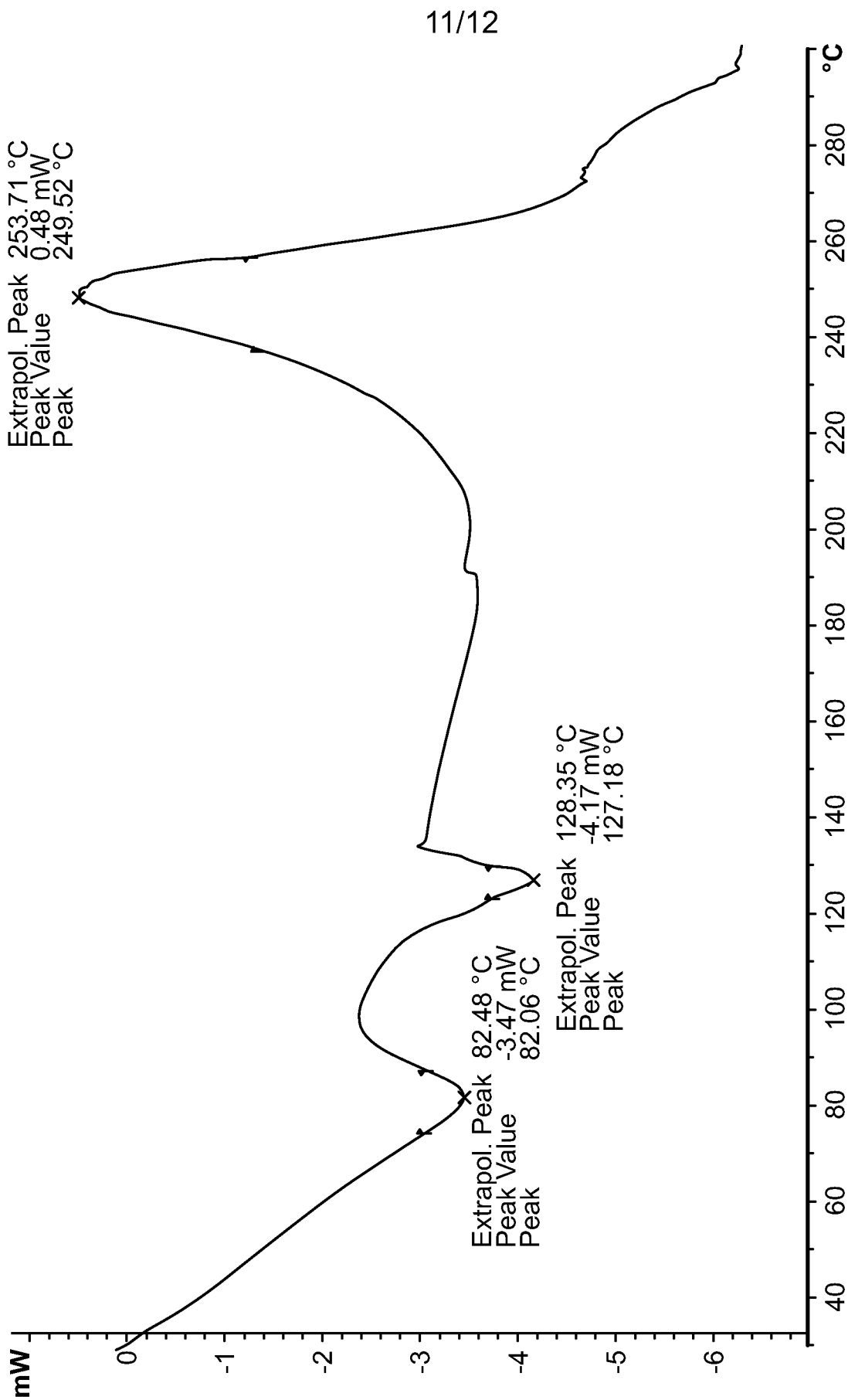


FIG. 11

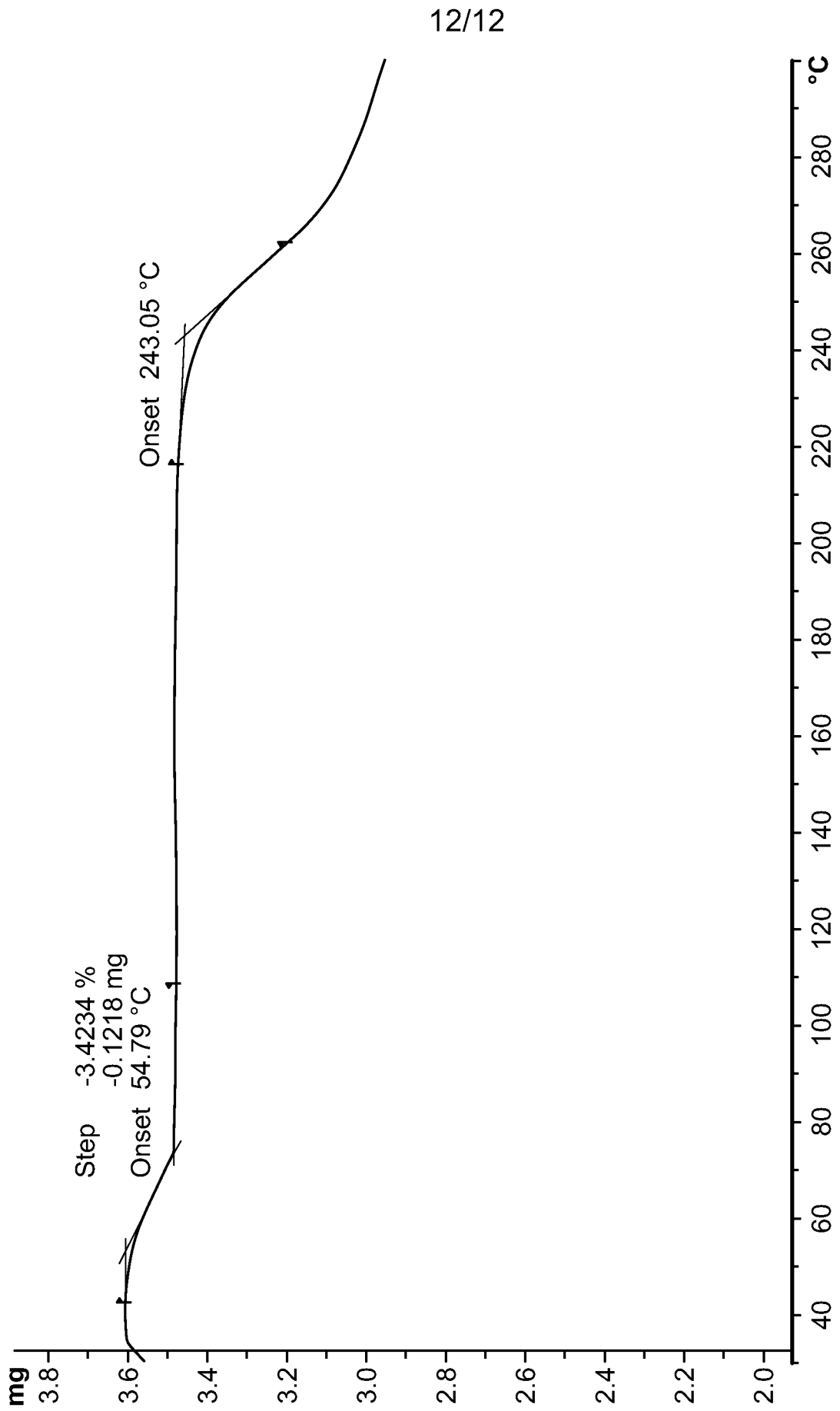


FIG. 12