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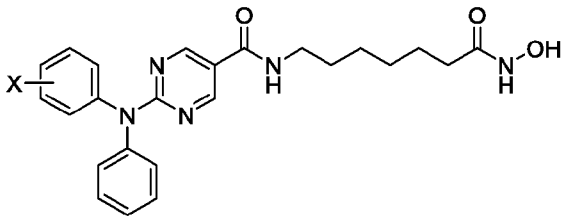
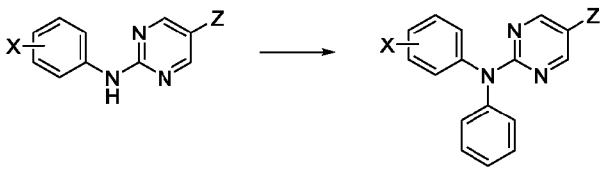
[Continued on next page]

(54) Title: METHODS OF MAKING PROTEIN DEACETYLASE INHIBITORS

(57) Abstract: The present invention relates to methods and intermediates useful for the synthesis of protein deacetylase inhibitors of formula (Ia) comprising the following step (11a) (3a).



(Ia)



11a 3a

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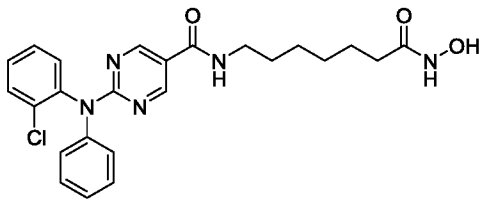
METHODS OF MAKING PROTEIN DEACETYLASE INHIBITORS

RELATED APPLICATION

This application claims priority to United States Provisional Application No. 62/172,624, filed on June 8, 2015, the content of which is incorporated herein by reference in its entirety.

BACKGROUND

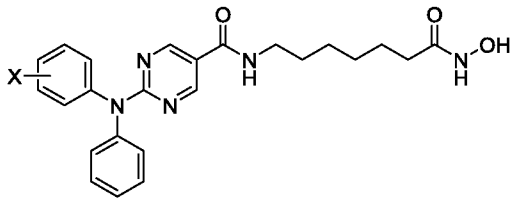


(I)

Compound (I) is disclosed in U.S. Patent No. 8,148,526 as an HDAC inhibitor. Example 2 of U.S. Patent Application Publication No. 2015/0099744 discloses a synthesis of compound (I). As detailed herein in Example 3, this synthesis procedure resulted in the formation of significant amounts of de-chlorination and chlorine-migration side products. These impurities have solubilities that are similar to the solubilities of the desired intermediates. Removal of the impurities is very challenging, requiring lengthy work-ups, involving numerous washes, triturations and crystallizations. Triturations, in particular, are known to be inefficient and unscalable processes. When compound (I) was prepared according to Example 2, the necessary purification steps resulted in a significant loss of desired intermdiates, led to a modest overall yield, and rendered further industrial scale up of the synthesis route unpractical. There remains a need for new methods for the synthesis of compound (I), and related compounds, that minimize the formation of impurities, and that are amenable to industrial scale-up.

SUMMARY

Accordingly, provided herein is an improved method of making compound (Ia).

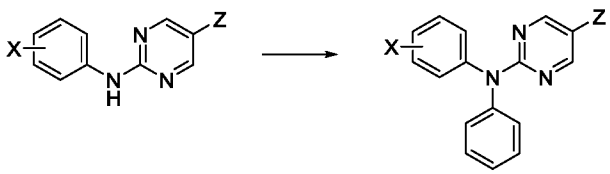


(Ia)

The improved method entirely avoids the formation of de-chlorination and chlorine-migration impurities. Moreover, the improved method results in a higher (e.g., over double) yield of compound (I) (e.g., 15.7% overall yield by the method of Example 2, versus 40% overall yield by the improved method). Also provided are compounds useful as intermediates in the synthesis of compound (Ia) and compositions comprising said compounds.

In one aspect, provided herein is a method of making compound (Ia), the method comprising the steps of:

converting compound 11a into compound 3a:



11a 3a ;

wherein X is selected from fluorine, chlorine, bromine and iodine;

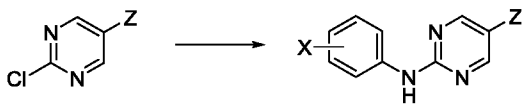
Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl; and

converting compound 3a into compound (Ia).

In one embodiment, compound 11a is prepared by a method comprising the step of:

converting compound 1a into compound 11a:



1a 11a ;

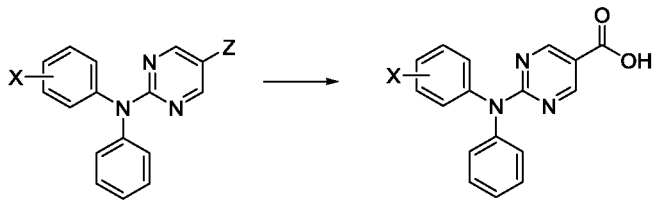
wherein X is selected from fluorine, chlorine, bromine and iodine;

Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl.

In another embodiment, the step of converting compound 3a into compound (Ia) comprises the steps of:

converting compound 3a into compound 4a:

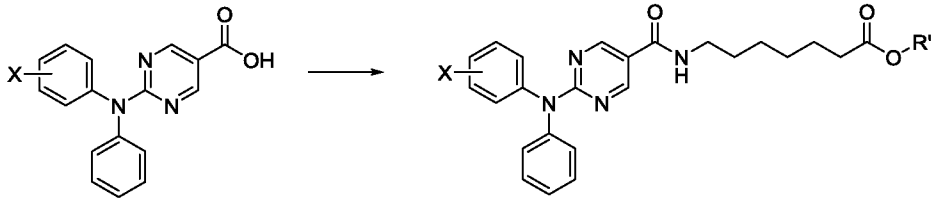


3a 4a ; and

converting compound 4a into compound (Ia).

In another embodiment, the step of converting compound 4a into compound (Ia) comprises the steps of:

converting compound 4a into compound 5a:

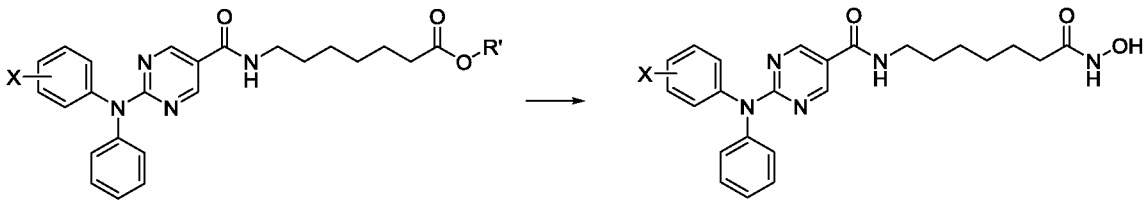


4a 5a ;

wherein X is selected from fluorine, chlorine, bromine and iodine; and

R' is C_1-C_6 alkyl; and

converting compound 5a into compound (Ia):

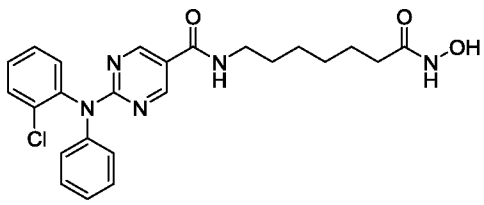


5a (Ia)

wherein X is selected from fluorine, chlorine, bromine and iodine.

In a particular embodiment of the method of making compound (Ia), X is chlorine. In another particular embodiment, Z is CO_2Et (i.e., R is ethyl). In another particular embodiment, R' is methyl.

In another aspect, provided herein is a method of making compound (I):

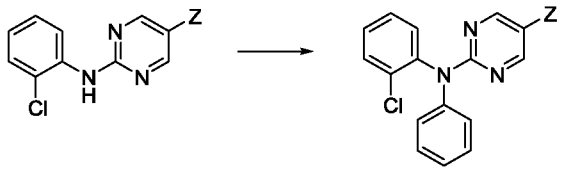


(I)

,

the method comprising the steps of:

converting compound 11b into compound 3b:



11b 3b

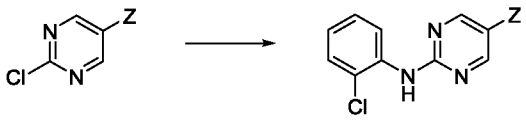
;

wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl; and

converting compound 3b into compound (I).

In one embodiment, compound 11b is prepared by a method comprising the step of:

converting compound 1b into compound 11b:

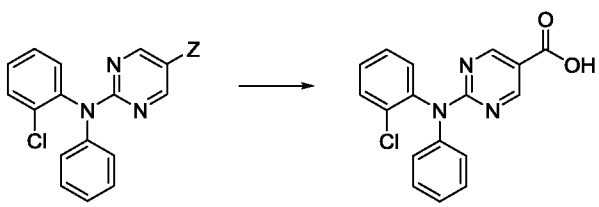


1b 11b

;

wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl.

In another embodiment, the step of converting compound 3b into compound (I) comprises the steps of: converting compound 3b into compound 4:

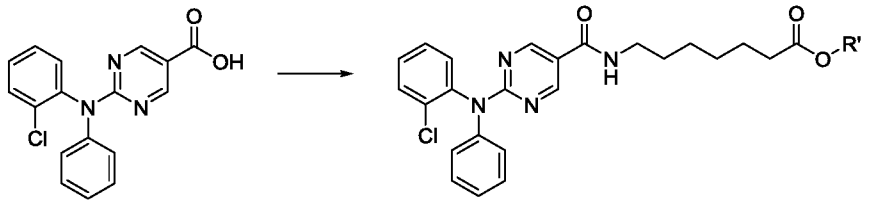


3b 4

; and

converting compound 4 into compound (I).

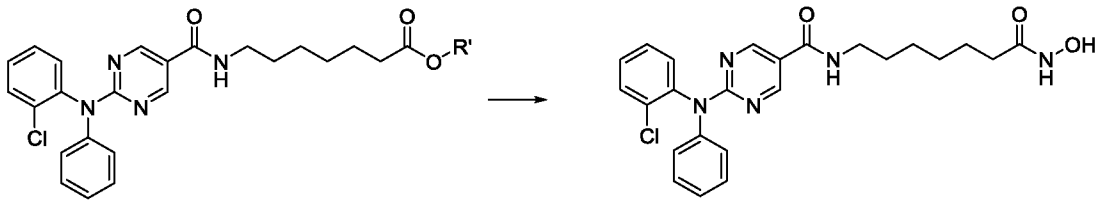
In another embodiment, the step of converting compound 4 into compound (I) comprises the steps of: converting compound 4 into compound 5b:



4 5b ;

wherein R' is C_1-C_6 alkyl; and

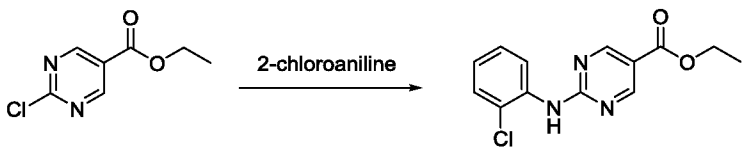
converting compound 5b into compound (I):



5b (I) .

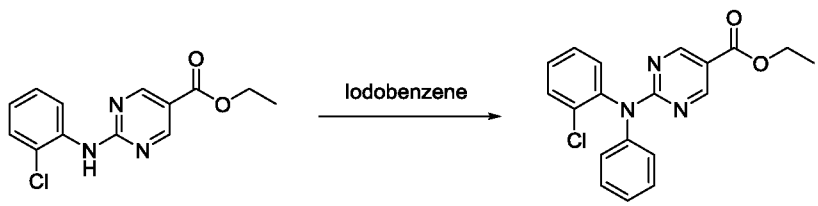
In a particular embodiment of the above methods, Z is CO_2Et (i.e., R is ethyl). In another particular embodiment, R' is methyl.

In a particular embodiment, the step of converting compound 1b into compound 11b comprises reacting compound 1 with 2-chloroaniline to obtain compound 11:



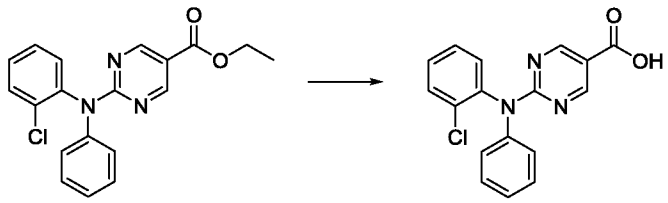
1 11 .

In another particular embodiment, the step of converting compound 11b into compound 3b comprises reacting compound 11 with iodobenzene to obtain compound 3:



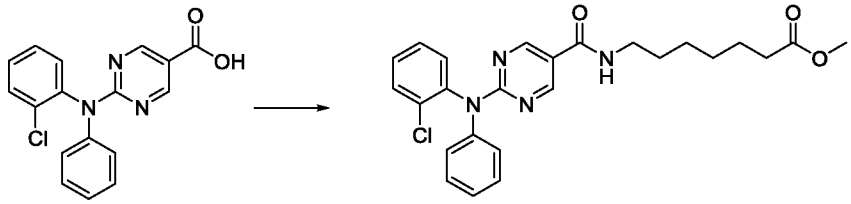
11 3 .

In another particular embodiment, the step of converting compound 3b into compound 4 comprises comprises hydrolyzing the ester of compound 3:



3 4

In another particular embodiment, the step of converting compound 4 into compound 5b comprises reacting compound 4 with methyl 7-aminoheptanoate to obtain compound 5:



4 5

In another particular embodiment, the step of converting compound 5b into compound (I) comprises reacting compound 5 with hydroxylamine, or a salt thereof, to obtain compound (I), or a salt thereof.

In another aspect, provided herein is a method of making compound (I) comprising the steps:

(1) reacting ethyl 2-chloropyrimidine-5-carboxylate with 2-chloroaniline to obtain compound 11;

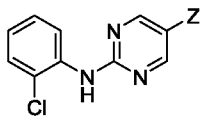
(2) reacting compound 11 with iodobenzene to obtain compound 3;

(3) reacting compound 3 with aqueous base, then with acid, to obtain compound 4;

(4) reacting compound 4 with methyl 7-aminoheptanoate to obtain compound 5; and

(5) reacting compound 5 with hydroxylamine, or a salt thereof, to obtain compound (I), or a salt thereof.

In another aspect, provided herein is a compound having the structure of 11b:



11b ;

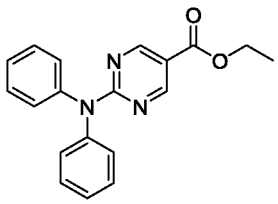
wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl. In one embodiment, Z is $–CO_2R$. In a particular embodiment, Z is $–CO_2R$ and R is ethyl. In another particular embodiment, compound 11b is compound 11.

In another aspect, provided herein is a composition comprising 1b and 11b, wherein 1b and 11b are defined above. In one embodiment of the composition, 1b is compound 1 and 11b is compound 11.

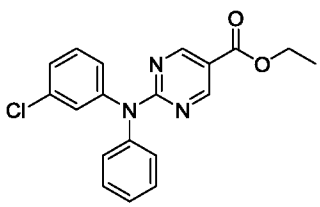
In another aspect, provided herein is a composition comprising 11b and 3b, wherein 11b and 3b are defined above. In one embodiment of the composition, 11b is compound 11 and 3b is compound 3.

In another aspect, provided herein is a composition comprising the compound 11b. In one embodiment, the composition further comprises compound 3.

In another aspect, provided herein is a composition comprising compound 3, wherein the composition is free from compounds de-Cl-3 and m-Cl-3:

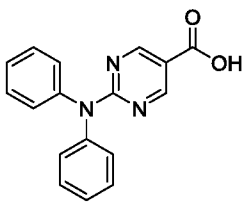


de-Cl-3

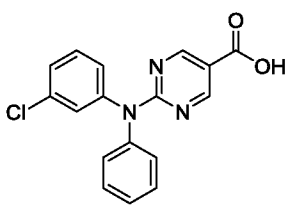


m-Cl-3

In another aspect, provided herein is a composition comprising compound 4, wherein the composition is free from compounds de-Cl-4 and m-Cl-4:

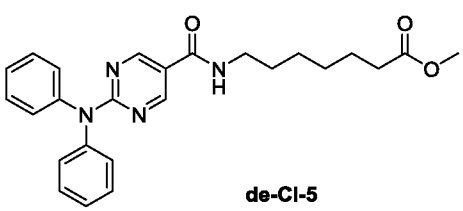


de-Cl-4

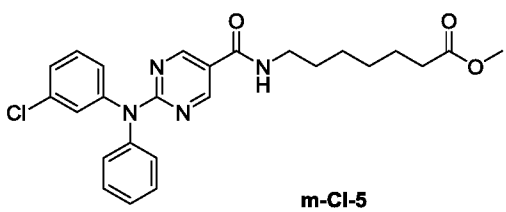


m-Cl-4

In another aspect, provided herein is a composition comprising compound 5, wherein the composition is free from compounds de-Cl-5 and m-Cl-5:



de-Cl-5



m-Cl-5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a generic synthesis of compound (I) according to the improved method described herein.

Figure 2 depicts a specific synthesis of compound (I) according to the improved method described herein.

Figure 3 depicts ^{1}HNMR data for compound 11.

Figure 4 depicts ^{1}HNMR data for compound 4.

Figure 5 depicts ^{1}HNMR data for compound 5.

Figure 6 depicts ^{1}HNMR data for compound (I).

Figure 7 depicts the correlation of ^{1}HNMR data to the structure of compound (I).

Figure 8 depicts the XRPD pattern (Pattern A) of compound (I), Form I.

Figure 9 depicts the DSC graph of compound (I), Form I.

Figure 10 depicts the TGA thermogram of compound (I), Form I.

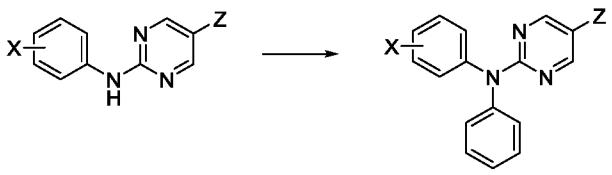
Figure 11 depicts the XRPD pattern (Pattern D) of compound (I), Form IV.

DETAILED DESCRIPTION OF THE INVENTION

Methods of Synthesis

Provided herein, inter alia, is a method of making compound (Ia) comprising the steps of:

converting compound 11a into compound 3a:



11a **3a** ;

wherein X is selected from fluorine, chlorine, bromine and iodine;

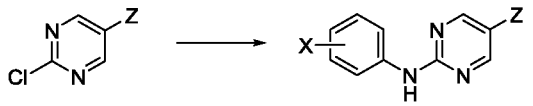
Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl; and

converting compound 3a into compound (Ia).

In one embodiment, compound 11a is prepared by a method comprising the step of:

converting compound 1a into compound 11a:



1a 11a ;

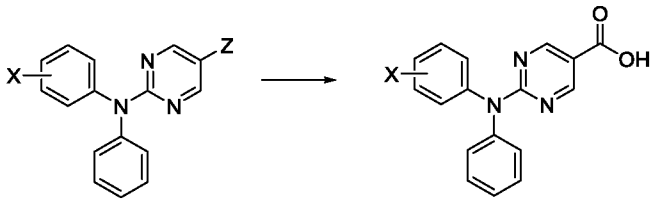
wherein X is selected from fluorine, chlorine, bromine and iodine;

Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl.

In another embodiment, the step of converting compound 3a into compound (Ia) comprises the steps of:

converting compound 3a into compound 4a:

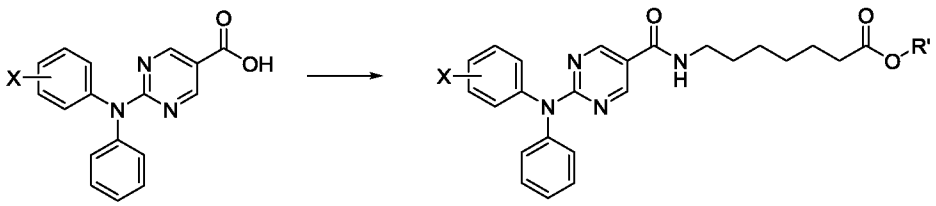


3a 4a ; and

converting compound 4a into compound (Ia).

In another embodiment, the step of converting compound 4a into compound (Ia) comprises the steps of:

converting compound 4a into compound 5a:

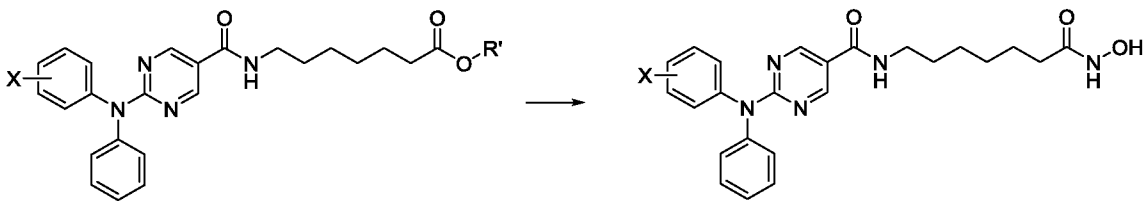


4a 5a ;

wherein X is selected from fluorine, chlorine, bromine and iodine; and

R' is C_1-C_6 alkyl; and

converting compound 5a into compound (Ia):



5a (Ia)

wherein X is selected from fluorine, chlorine, bromine and iodine.

In a particular embodiment of the method of making compound (Ia), X is chlorine. In another particular embodiment, Z is CO_2Et (i.e., R is ethyl). In another particular embodiment, R' is methyl.

With reference to Figure 1, provided herein is a method of making compound (I), wherein Z is selected from the group consisting of –CN and $–CO_2R$, R is C_1-C_6 alkyl, and R' is C_1-C_6 alkyl. In certain embodiments of the method, R is C_1-C_6 alkyl. In a particular embodiment, R is ethyl. In another particular embodiment, R' is methyl.

In one embodiment, the method comprises the step of converting compound 1b to compound 11b, i.e., *Step (1)*. In a particular embodiment, *Step (1)* comprises reacting compound 1b with 2-chloroaniline to obtain compound 11b.

In another embodiment, the method comprises the step of converting compound 11b to compound 3b, i.e., *Step (2)*. In a particular embodiment, *Step (2)* comprises reacting compound 11b with iodobenzene to obtain compound 3b.

In another embodiment, the method comprises *Steps (1)-(2)*, and the step of converting compound 3b to compound 4, i.e., *Step (3)*. In a particular embodiment, *Step (3)* comprises forming a mixture of the product of *Step (2)* (i.e., the reaction mixture comprising compound 3b) and water, and heating the mixture.

In another embodiment, the method comprises *Steps (1)-(3)*, and the step of converting compound 4 to compound 5b, i.e., *Step (4)*. In a particular embodiment, *Step (4)* comprises reacting compound 4 with an ester of 7-aminoheptanoic acid to obtain compound 5b.

In another embodiment, the method comprises *Steps (1)-(4)*, and the step of converting compound 5b to compound (I), i.e., *Step (5)*. In a particular embodiment, *Step (5)* comprises reacting compound 5b with hydroxylamine, or a salt thereof, to obtain compound (I), or a salt thereof.

In another embodiment, the method comprises *Steps (1)-(5)*.

In another embodiment, the method comprises *Steps (1)-(2)*, with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed. In another embodiment, the method comprises *Steps (1)-(3)* with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed. In another embodiment, the method comprises *Steps (1)-(4)* with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed.

With reference to Figure 2, provided herein is a method of making compound (I). In one embodiment, the method comprises the step of converting compound 1 to compound 11, i.e., *Step (1)*. In a particular embodiment, *Step (1)* comprises reacting ethyl 2-chloropyrimidine-5-carboxylate with 2-chloroaniline. In another embodiment, *Step (1)* comprises the use of an alcohol solvent (particularly, e.g., ethanol). In another embodiment, *Step (1)* comprises the use of elevated temperatures (particularly, e.g., about 78 °C). In another particular embodiment, *Step (1)* comprises the conditions disclosed in Example 4. In another particular embodiment, *Step (1)* comprises the conditions disclosed in Example 5. In still another embodiment, *Step (1)* produces compound 11 in at least about 81% yield (e.g., in about 81% yield).

In another embodiment, the method comprises the step of converting compound 11 to compound 3, i.e., *Step (2)*. In another embodiment, *Step (2)* comprises the use of a polar aprotic solvent (particularly, e.g., dimethylsulfoxide). In another embodiment, *Step (2)* comprises the use of elevated temperatures (particularly, e.g., about 120 ± 5 °C). In a particular embodiment, *Step (2)* comprises reacting compound 11 with iodobenzene. In another particular embodiment, *Step (2)* comprises reacting compound 11 with iodobenzene in presence of copper. In still another particular embodiment, *Step (2)* comprises reacting compound 11 with iodobenzene in presence of copper and potassium carbonate. In another particular embodiment, *Step (2)* comprises the conditions disclosed in Example 4. In another particular embodiment, *Step (2)* comprises the conditions disclosed in Example 5.

In another embodiment, the method comprises *Steps (1)-(2)*, and the step of converting compound 3 to compound 4, i.e., *Step (3)*. In a particular embodiment, *Step (3)* comprises forming a mixture of the product of *Step (2)* (i.e., the reaction mixture comprising compound 3) and water. In another embodiment, *Step (3)* comprises the use of elevated temperatures (particularly, e.g., about 90-100 °C). In another particular embodiment, *Step (3)* comprises the conditions disclosed in Example 4. In another particular embodiment, *Step (3)* comprises the conditions disclosed in Example 5. In still another embodiment, *Steps (2)-(3)* produce compound 4 from compound 11 in at least about 65% yield (e.g., in about 65% yield). In yet another embodiment, *Steps (2)-(3)* produce compound 4 from compound 11 in at least about 81% yield (e.g., in about 81% yield).

In another embodiment, the method comprises *Steps (1)-(3)*, and the step of converting compound 4 to compound 5, i.e., *Step (4)*. In another embodiment, *Step (3)* comprises the use of a polar aprotic solvent (particularly, e.g., dimethylformamide). In a

particular embodiment, *Step (4)* comprises the use of dimethylformamide and dichloromethane. In a particular embodiment, *Step (4)* comprises reacting compound 4 with methyl 7-aminoheptanoate, or a salt thereof. In another particular embodiment, *Step (4)* comprises converting compound 4 to an activated acid derivative, then reacting the activated acid derivative with methyl 7-aminoheptanoate. In a particular embodiment, the activated acid derivative is an acid chloride. In another particular embodiment, *Step (4)* comprises the conditions disclosed in Example 4. In another particular embodiment, *Step (4)* comprises the conditions disclosed in Example 5.

In another embodiment, the method comprises *Steps (1)-(4)*, and the step of converting compound 5 to compound (I), i.e., *Step (5)*. In another embodiment, *Step (5)* comprises the use of lowered temperatures (particularly, e.g., about 0-5 °C, or about 0-10 °C, or about 0±5 °C). In a particular embodiment, *Step (5)* comprises reacting compound 5 with hydroxylamine, or a salt thereof. In another particular embodiment, *Step (5)* comprises the use of an alkoxide base in an alcohol solvent (particularly, e.g., sodium methoxide in methanol). In another embodiment, *Step (5)* comprises crystallizing crude compound (I) from a solvent comprising a C_1-C_6 alcohol to obtain Form I. In a particular embodiment, the solvent is isopropanol. In another particular embodiment, the solvent is 1-propanol/water. In another particular embodiment, *Step (5)* comprises the conditions disclosed in Example 4. In another particular embodiment, *Step (5)* comprises the conditions disclosed in Example 5.

In another embodiment, the method comprises *Steps (1)-(5)*.

In another embodiment, the method comprises *Steps (1)-(2)*, with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed. In another embodiment, the method comprises *Steps (1)-(3)* with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed. In another embodiment, the method comprises *Steps (1)-(4)* with subsequent steps known in the art, such that compound (I), or a salt thereof, is formed.

The methods of making compound (I) are superior to previous methods, at least for the following reasons. In contrast to the method of Examples 2 and 3, the claimed methods involve introduction of the chlorine atom in Step (1). This step does not involve conditions under which the aryl chloride is reactive. Accordingly, the chloride moiety is not subject to copper-mediated migration and/or dechlorination. Analysis of Step (1) by high performance liquid chromatography (HPLC) reveals the reaction mixture is free from such migration and/or dechlorination side products.

Compounds and Compositions

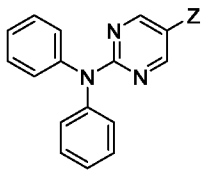
With reference to Figures 2 and 3, provided herein are compounds useful as intermediates in the synthesis of compound (I). In one aspect, provided herein is the compound 11b, wherein Z is selected from the group consisting of –CN and $–CO_2R$, and wherein R is C_1-C_6 alkyl. In a particular embodiment, Z is $–CO_2R$. In another particular embodiment, Z is $–CO_2Et$.

In another aspect, provided herein is the compound 11.

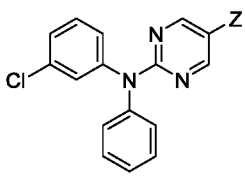
Also provided herein are compositions useful in the synthesis of compound (I). In one aspect, provided herein as a composition comprising compounds 1b and 11b, wherein Z is defined according to the embodiments above. In a particular embodiment, Z is $–CO_2R$. In another particular embodiment, Z is $–CO_2Et$. In another embodiment, the composition further comprises 2-chloroaniline.

In another aspect, provided herein is a composition comprising compounds 1 and 11. In one embodiment, the composition further comprises 2-chloroaniline. In another embodiment, the composition further comprises reagents specified in Example 4.

In another aspect, provided herein is a composition comprising compounds 11b and 3b, wherein Z is defined according to the embodiments above. In a particular embodiment, Z is $–CO_2R$. In another particular embodiment, Z is $–CO_2Et$. In one embodiment, the composition further comprises compound 11b. In another embodiment, the composition further comprises iodobenzene. In another embodiment, the composition is free from dechlorination and chlorine-migration impurities, such as de-Cl-3b and m-Cl-3b:

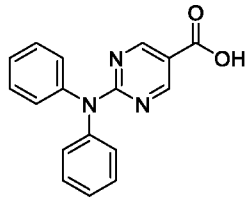


de-Cl-3b

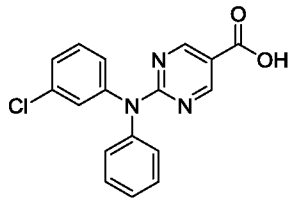


m-Cl-3b

wherein Z is defined according to the embodiments above. In another embodiment, the composition further comprises compound 4, or a salt thereof, and is free from dechlorination and chlorine-migration impurities, such as de-Cl-4 and m-Cl-4, or salts thereof:

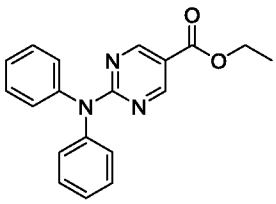


de-Cl-4

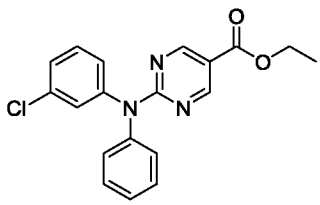


m-Cl-4

In another aspect, provided herein is a composition comprising compounds 11 and 3. In one embodiment, the composition further comprises iodobenzene. In another embodiment, the composition is free from dechlorination and chlorine-migration impurities, such as de-Cl-3 and m-Cl-3:



de-Cl-3



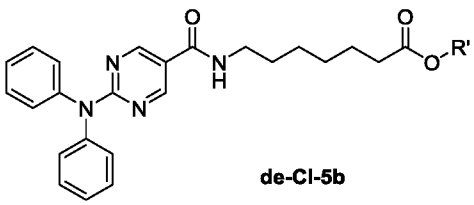
m-Cl-3

In another embodiment, the composition further comprises compound 4, or a salt thereof, and is free from dechlorination and chlorine-migration impurities, such as de-Cl-4 and m-Cl-4, or salts thereof.

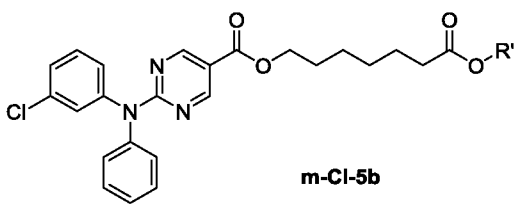
In another aspect, provided herein is a composition comprising compound 4 and one or more compounds selected from 1b, 11b and 3b, wherein Z is defined according to the embodiments above. In a particular embodiment, Z is $-CO_2R$. In another particular embodiment, Z is $-CO_2Et$.

In another aspect, provided herein is a composition comprising compound 4 and one or more compounds selected from compounds 1, 11 and 3.

In another aspect, provided herein is a composition comprising compound 5b and less than about 1% (combined area percentage as measured by HPLC) of compounds de-Cl-5b and m-Cl-5b:



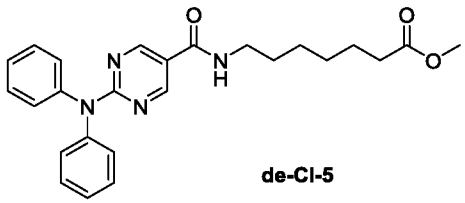
de-Cl-5b



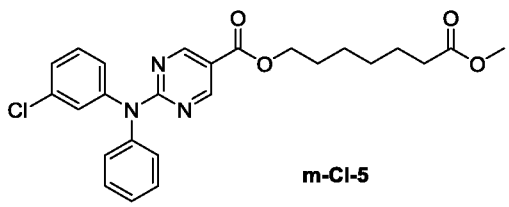
m-Cl-5b

wherein R' is defined according to the embodiments above. In one embodiment, the composition is free from de-Cl-5b and m-Cl-5b.

In another aspect, provided herein is a composition comprising compound 5 and less than about 1% (combined area percentage as measured by HPLC) of compounds de-Cl-5 and m-Cl-5:



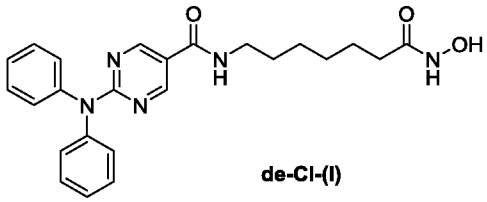
de-Cl-5



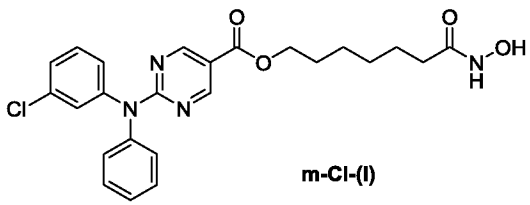
m-Cl-5

In one embodiment, the composition is free from de-Cl-5 and m-Cl-5.

In another aspect, provided herein is a composition comprising compound 5, compound (I) and less than about 1% (combined area percentage as measured by HPLC) of compounds de-Cl-(I) and m-Cl-(I):



de-Cl-(I)



m-Cl-(I)

In one embodiment, the composition is free from de-Cl-(I) and m-Cl-(I).

Definitions

Acids and bases useful in the methods herein are known in the art. Acid catalysts are any acidic chemical, which can be inorganic (e.g., hydrochloric, sulfuric, nitric acids, aluminum trichloride) or organic (e.g., camphorsulfonic acid, p-toluenesulfonic acid, acetic acid, ytterbium triflate) in nature. Acids are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions. Bases are any basic chemical, which can be inorganic (e.g., sodium bicarbonate, potassium hydroxide) or organic (e.g., triethylamine, pyridine) in nature. Bases are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety. Preferably the alkyl comprises 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl).

As used herein, the term "react" or "reacting" refers to the formation of a bond between two or more reactant compounds to produce a product compound. For example, a first compound and a second compound may react to form a product compound, wherein the product compound comprises a portion of the first compound and a portion of the second

compound, wherein the two portions are joined by a covalent bond. The term "reacting" does not refer to the interaction of solvents, catalysts, ligands, or other components that may serve to promote the occurrence of the reaction between the compounds.

As used herein, the terms "salt thereof" or "salts thereof" may refer to acid addition salts, metal salts, or ammonium salts. Such salts can be formed by procedures well known and described in the art. Acid addition salts may be formed from inorganic acids, e.g. hydrochloric, hydrobromic, sulphuric or phosphoric acids, and organic acids, e.g. succinic, malaeic, tartaric, acetic, oxalic or fumaric acid. Examples of addition salts include, without limitation, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

As used herein, the term "copper" can refer to Cu(0), Cu(I) or Cu(II). Non-limiting examples of copper include Cu(0) powder, copper-bronze, cupric oxide, cupric chloride, cupric iodide, cuprous chloride, cuprous iodide and other forms or salts of copper that are known by those of skill in the art.

As used herein, the term "activated acid derivative" refers to a derivative of a carboxylic acid that is susceptible to nucleophilic acyl substitution, for example, by virtue of having a leaving group on the carbonyl carbon. Non-limiting examples of activated acid

derivatives include acyl halides (also referred to as acid chlorides), carboxylic acid anhydrides (including, for example, mixed carboxylic acid anhydrides), acyl imidazoles (prepared, for example, by reaction of a carboxylic acid with carbonyl diimidazole), and O-acyl isoureas (prepared, for example, by reaction of a carboxylic acid with a carbodiimide reagent such as EDC or DCC).

Compositions and mixtures that are "free from" a particular solute or substance may comprise less than 5% (e.g., less than 4%, less than 3%, less than 2%, less than 1%, less than 0.1% or less than 0.01%) by weight of the solute or substance. In one embodiment, compositions and mixtures that are "free from" a particular solute or substance comprise an amount of the solute or substance that is below the limit of detection of the analytical instrumentation described herein.

Incorporation by Reference

The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended with be encompassed by the claims.

EXAMPLES

Instrumentation and Methods

Differential Scanning Calorimetry (DSC) data were collected using a TA Instruments Q10 DSC. Approximately, samples (2-8 mg) were placed in unsealed but covered hermetic alodined aluminum sample pans and scanned from 30 to 300 °C at a rate of 10 °C/min under a nitrogen purge of 50 mL/min.

Thermal Gravimetric Analysis (TGA) data were collected using a TA Instruments TGA Q500. Approximately, 5-10 mg samples were placed in an open, pre-tared aluminum

sample pan and scanned from 25 to 300 °C at a rate of 10 °C/min using a nitrogen purge at 60 mL/min.

X-ray Powder Diffractometer (XRPD) patterns were obtained using a Bruker D8 Advance equipped with a Cu Kα radiation source (λ=1.54 °A), a 9-position sample holder and a LYNXEYE super speed detector. Samples were placed on zero-background, silicon plate holders for analysis.

Dynamic Vapor Soprtion (DVS) analysis was performed using an Aquadyne DVS-2 gravimetric water sorption analyzer. The relative humidity was adjusted between 2-95% and the weight of the sample was continuously monitored and recorded with respect to the relative humidity and time.

Proton Nuclear Magnetic Resonance (^{1}H-NMR): Samples were prepared by dissolving the compound in deuterated dimethylsulfoxide with 0.05% (v/v) tetramethylsilane (TMS). Spectra were collected at ambient temperature on a Bruker Avance 300 MHz NMR equipped with TopSpin software. The number of scans was 16 for ^{1}H-NMR.

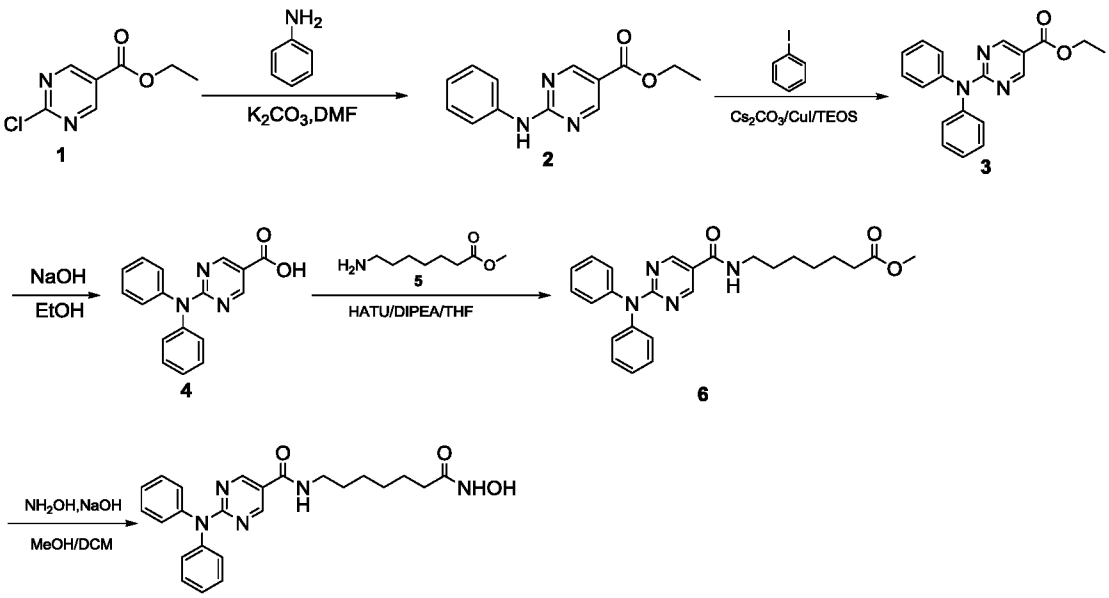
Karl Fischer (KF): The apparent water content in samples was determined by Karl Fischer titration using a Mettler Toledo DL39 Coulometric KF Titrator. HYDRANAL-Coulomat AD was used as the titrant. About 20 mg of the solid was used for titration. The analytical parameters are presented in Table 1.

Table 1.

KF Parameter	Value
Speed [%]	40
Mix time [sec]	10
Auto start	No
Blank [µg]	0
Drift [µg/min]	5
Calculation	Ug
Standby	Yes
Initial drift [µg/min]	<10
Initial Potential [mV]	100

Example 1: Comparative Synthesis of 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl) pyrimidine-5-carboxamide

Reaction Scheme



Synthesis of Intermediate 2: A mixture of aniline (3.7 g, 40 mmol), compound 1 (7.5 g, 40 mmol), and K_2CO_3 (11 g, 80 mmol) in DMF (100 ml) was degassed and stirred at 120 °C under N_2 overnight. The reaction mixture was cooled to r.t. and diluted with EtOAc (200 ml), then washed with saturated brine (200 ml × 3). The organic layers were separated and dried over Na_2SO_4, evaporated to dryness and purified by silica gel chromatography (petroleum ethers/EtOAc = 10/1) to give the desired product as a white solid (6.2 g, 64 %).

Synthesis of Intermediate 3: A mixture of compound 2 (6.2 g, 25 mmol), iodobenzene (6.12 g, 30 mmol), CuI (955 mg, 5.0 mmol), Cs_2CO_3 (16.3 g, 50 mmol) in TEOS (200 ml) was degassed and purged with nitrogen. The resulting mixture was stirred at 140 °C for 14 hrs. After cooling to r.t., the residue was diluted with EtOAc (200 ml). 95% EtOH (200 ml) and NH_4F-H_2O on silica gel [50g, pre-prepared by the addition of NH_4F (100g) in water (1500 ml) to silica gel (500g, 100-200 mesh)] was added, and the resulting mixture was kept at r.t. for 2 hrs. The solidified materials were filtered and washed with EtOAc. The filtrate was evaporated to dryness and the residue was purified by silica gel chromatography (petroleum ethers/EtOAc = 10/1) to give a yellow solid (3 g, 38%).

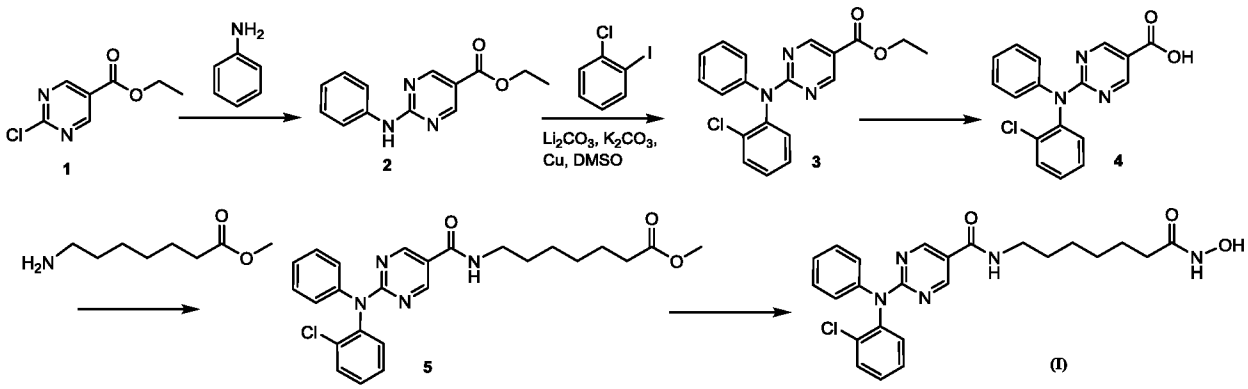
Synthesis of Intermediate 4: 2N NaOH (200 ml) was added to a solution of compound 3 (3.0 g, 9.4 mmol) in EtOH (200 ml). The mixture was stirred at 60 °C for 30min. After evaporation of the solvent, the solution was neutralized with 2N HCl to give a white precipitate. The suspension was extracted with EtOAc (2 × 200 ml), and the organic layers were separated, washed with water (2 × 100 ml), brine (2 × 100 ml), and dried over Na_2SO_4. Removal of the solvent gave a brown solid (2.5 g, 92 %).

Synthesis of Intermediate 6: A mixture of compound 4 (2.5 g, 8.58 mmol), compound 5 (2.52 g, 12.87 mmol), HATU (3.91 g, 10.30 mmol), and DIPEA (4.43 g, 34.32 mmol) was stirred at r.t. overnight. After the reaction mixture was filtered, the filtrate was evaporated to dryness and the residue was purified by silica gel chromatography (petroleum ethers/EtOAc = 2/1) to give a brown solid (2 g, 54 %).

Synthesis of 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide: A mixture of the compound 6 (2.0 g, 4.6 mmol), sodium hydroxide (2N, 20 mL) in MeOH (50 ml) and DCM (25 ml) was stirred at 0 °C for 10 min. Hydroxylamine (50%) (10 ml) was cooled to 0 °C and added to the mixture. The resulting mixture was stirred at r.t. for 20 min. After removal of the solvent, the mixture was neutralized with 1M HCl to give a white precipitate. The crude product was filtered and purified by pre-HPLC to give a white solid (950 mg, 48%).

Example 2: Comparative Synthesis of 2-((2-chlorophenyl)(phenyl)amino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide - Compound (I)

Reaction Scheme



Step (1)

Synthesis of Intermediate 2: A mixture of aniline (3.7 g, 40 mmol), ethyl 2-chloropyrimidine-5-carboxylate 1 (7.5 g, 40 mmol), K_2CO_3 (11 g, 80 mmol) in DMF (100 ml) was degassed and stirred at 120 °C under N_2 overnight. The reaction mixture was cooled to rt and diluted with EtOAc (200 ml), then washed with saturated brine (200 ml x 3). The organic layer was separated and dried over Na_2SO_4, evaporated to dryness and purified by silica gel chromatography (petroleum ethers/EtOAc = 10/1) to give the desired product as a white solid (6.2 g, 64 %).

Step (2)

Synthesis of Intermediate 3: A mixture of compound 2 (69.2 g, 1 equiv.), 1-chloro-2-iodobenzene (135.7 g, 2 equiv.), Li_2CO_3 (42.04 g, 2 equiv.), K_2CO_3 (39.32 g, 1 equiv.), Cu (1 equiv. 45 μm) in DMSO (690 ml) was degassed and purged with nitrogen. The resulting mixture was stirred at 140 °C for 36 hours. Work-up of the reaction gave compound 3 at 93 % yield.

Step (3)

Synthesis of Intermediate 4: 2N NaOH (200 ml) was added to a solution of the compound 3 (3.0 g, 9.4 mmol) in EtOH (200 ml). The mixture was stirred at 60 °C for 30min. After evaporation of the solvent, the solution was neutralized with 2N HCl to give a white precipitate. The suspension was extracted with EtOAc (2 x 200 ml), and the organic layer

was separated, washed with water (2 x 100 ml), brine (2 x 100 ml), and dried over Na_2SO_4. Removal of solvent gave a brown solid (2.5 g, 92 %).

Step (4)

Synthesis of Intermediate 5: A procedure analogous to the Synthesis of Intermediate 6 in Example 1 was used.

Step (5)

Synthesis of 2-((2-chlorophenyl)(phenyl)amino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide: A procedure analogous to the Synthesis of 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide in Example 1 was used.

Example 3: Process development for Steps 2-3 of Example 2

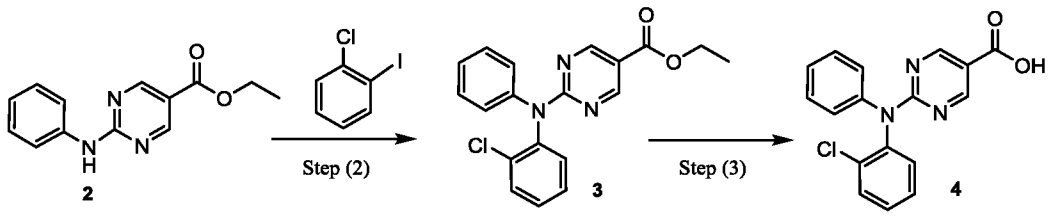


Table 2. Reactants and reagents

No.	Cpd 2	2-Cl-iodo -benzene	Solvent	Base	Catalyst	Temp. (°C)
1	2.43g (1.0eq)	4.77g (2.0eq)	25mL	Li_2CO_3 (2.22g, 3eq)	Cu (1.0 eq,106μm)	130 °C
2	24.3g (1.0eq)	47.7g (2.0eq)	240mL	Li_2CO_3 (22.2g, 3eq)	Cu (1.0 eq,106μm)	130-150 °C
3	24.3g (1.0eq)	47.7g (2.0eq)	240mL	Li_2CO_3 (22.2g, 3eq)	Cu (1.0 eq,106μm)	150 °C
4	24.3g (1.0eq)	47.7g (2.0eq)	150mL	Li_2CO_3 (22.2g, 3eq); after 42h, K_2CO_3	Cu (1.0 eq,45μm)	150 °C

				(13.8, 1eq)		
5	24.3g (1.0eq)	47.7g (2.0eq)	240mL	Li_2CO_3 (22.2g, 2eq) K_2CO_3 (19.65, 1eq)	Cu (1.0 eq,45μm)	140 °C
6	69.2g (1.0eq)	135.7g (2.0eq)	690mL	Li_2CO_3 (42.04g, 2eq) K_2CO_3 (39.32g, 1eq)	Cu (1.0 eq,45μm)	140 °C

Table 3. Results

No.	Conversion (%)	*m*-Cl 3/4	*de*-Cl 3/4
1	91.7%	1.43%	--
2	84.2%	1.92%	--
3	70.6%	2.19%	--
4	94.4%	7.88%	3.0%
5	89.4%	7.63%	1.08%
6	93%	8.5%	1.6%

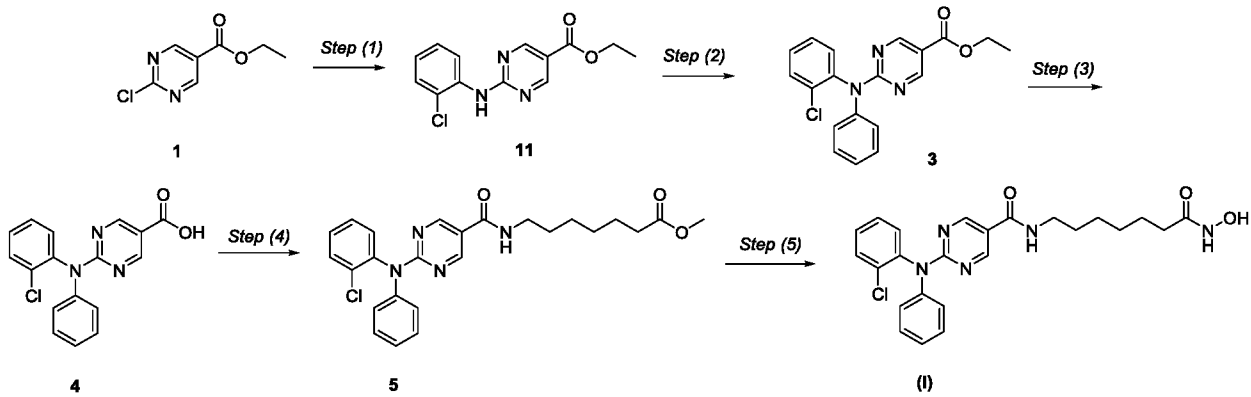
Table 4. Purification of Compound 4 by extraction and slurry

Purification Conditions	Results			HPLC
	de-Cl-4	*m-Cl-4*	*Compound 4*	
Crude Product	3.69%	3.53%	89.53%	
MTBE/Heptane (5vol/15vol)	2.93%	2.57%	93.34%	
iPrOH/H_2O (1vol/2vol)	3.55%	3.27%	91.41%	
EtOAc/PE (10vol/10vol)	3.87%	1.43%	93.48%	

MTBE/Heptane (10vol/10vol)	2.83%	2.67%	92.57%	
MEK/*Heptane* (3vol/6vol)	4.42%	3.16%	90.00%	
EtoAc	3.87%	1.43%	93.48%	
iProAc	3.91%	2.81%	90.91%	

Example 4: Improved synthesis of Compound (I)

Reaction Scheme



Step (1)

Synthesis of Compound 11: Ethyl 2-chloropyrimidine-5-carboxylate (ACY-5, 7.0 Kgs), ethanol (60 Kgs), 2-Chloroaniline (9.5 Kgs, 2 eq) and acetic acid (3.7 Kgs, 1.6 eq) were charged to a reactor under inert atmosphere. The mixture was heated to reflux. After at least 5 hours the reaction was sampled for HPLC analysis (method TM-113.1016). When analysis indicated reaction completion (< 1% ACY-5), the mixture was cooled to 70 ± 5 °C and N,N-Diisopropylethylamine (DIPEA) was added. The reaction was then cooled to 20 ± 5°C and the mixture was stirred for an additional 2-6 hours. The resulting precipitate is filtered and washed with ethanol (2 x 6 Kgs) and heptane (24 Kgs). The cake is dried under reduced pressure at 50 ± 5 °C to a constant weight to produce 8.4 Kgs compound 11 (81% yield and 99.9% purity (method TM-113.1016)). See ^{1}HNMR data in Figure 3.

Step (2)

Synthesis of Compound 3: Copper powder (0.68 Kgs, 1 eq, <75 micron), potassium carbonate (4.3 Kgs, 3.0 eq), and dimethyl sulfoxide (DMSO, 12.3 Kgs) were added to a reactor (vessel A). The resulting solution was heated to 120 ± 5°C. In a separate reactor (vessel B), a solution of compound 11 (2.9 Kgs) and iodobenzene (4.3 Kgs, 2 eq) in DMSO (5.6 Kgs) was

heated at 40 ± 5°C. The mixture was then transferred to vessel A over 2-3 hours. The reaction mixture was heated at 120 ± 5°C for 8-24 hours, until HPLC analysis (method TM-113.942) determined that ≤ 1% compound 11 was remaining.

Step (3)

Synthesis of Compound 4: The mixture of Step (2) was cooled to 90-100 °C and purified water (59 Kgs) was added. The reaction mixture was stirred at 90-100 °C for 2-8 hours until HPLC (method TM-113.942-see step 2) showed that ≤1% compound 3 was remaining. The reactor was cooled to 25 °C. The reaction mixture was filtered through Celite, then a 0.2 micron filter, and the filtrate was collected. The filtrate was extracted with methyl t-butyl ether twice (2 x 12.8 Kgs). The aqueous layer was cooled to 0-5 °C, then acidified with 6N hydrochloric acid (HCl) to pH 2-3 while keeping the temperature < 25°C. The reaction was then cooled to 5-15 °C. The precipitate was filtered and washed with cold water. The cake was dried at 45-55 °C under reduced pressure to constant weight to obtain 2.2 kg (65% yield) compound 4 in 90.3% AUC purity (method TM-113.942-see step 2). No dechlorinated product or Cl-migration product (i.e., de-Cl-4 or m-Cl-4) was observed. See ^{1}HNMR data in Figure 4.

Step (4)

Synthesis of Compound 5: Dichloromethane (40.3 Kgs), DMF (33g, 0.04 eq) and compound 4 (2.3 Kg) were charged to a reaction flask. The solution was filtered through a 0.2 µm filter and was returned to the flask. Oxalyl chloride (0.9 Kgs, 1 eq) was added via addition funnel over 30-120 minutes at < 30 °C. The batch was then stirred at < 30°C until reaction completion (compound 4 ≤3 %) was confirmed by HPLC (method TM-113.946). Next, the dichloromethane solution was concentrated and residual oxalyl chloride was removed under reduced pressure at < 40 °C. When HPLC analysis (method TM-113.946) indicated that < 0.10% oxalyl chloride was remaining, the concentrate was dissolved in fresh dichloromethane (24 Kgs) and transferred back to the reaction vessel (Vessel A).

A second vessel (Vessel B) was charged with Methyl 7-aminoheptanoate hydrochloride (Compound A1, 1.5 Kgs, 1.09 eq), DIPEA (2.5 Kgs, 2.7 eq), 4 (Dimethylamino)pyridine (DMAP, 42g, 0.05 eq), and DCM (47.6 Kgs). The mixture was cooled to 0-10 °C and the acid chloride solution in Vessel A was transferred to Vessel B while maintaining the temperature at 5 °C to 10 °C. The reaction is stirred at 5-10 °C for 3 to

24 hours at which point HPLC analysis indicated reaction completion (method TM-113.946, compound 4 ≤5%). The mixture was then extracted with a 1M HCl solution (20 Kgs), purified water (20 Kgs), 7% sodium bicarbonate (20 Kgs), purified water (20 Kgs), and 25% sodium chloride solution (20 Kgs). The dichloromethane was then vacuumdistilled at < 40 ºC and chased repeatedly with isopropyl alcohol. When analysis indicated that <1 mol% DCM was remaining, the mixture was gradually cooled to 0-5 °C and was stirred at 0-5 °C for an at least 2 hours. The resulting precipitate was collected by filtration and washed with cold isopropyl alcohol (6.4 Kgs). The cake was sucked dry on the filter for 4-24 hours, then was further dried at 45-55 °C under reduced pressure to constant weight. 2.2 Kgs (77% yield) was isolated in 95.9% AUC purity (method TM-113.953) and 99.9 wt %. See ^{1}HNMR data in Figure 5.

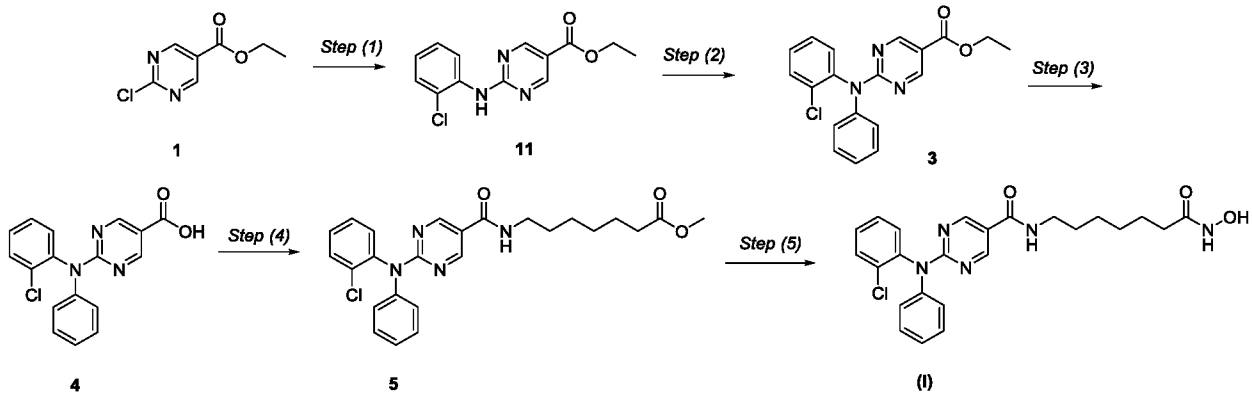
Step (5)

Synthesis of Compound (I): Hydroxylamine hydrochloride (3.3 Kgs, 10 eq) and methanol (9.6 Kgs) were charged to a reactor. The resulting solution was cooled to 0-5 °C and 25% sodium methoxide (11.2 Kgs, 11 eq) was charged slowly, maintaining the temperature at 0-10 °C. Once the addition was complete, the reaction was mixed at 20 °C for 1-3 hours and filtered, and the filter cake was washed with methanol (2 x 2.1 Kgs). The filtrate (hydroxylamine free base) was returned to the reactor and cooled to 0±5°C. Compound 5 (2.2 Kgs) was added. The reaction was stirred until the reaction was complete (method TM-113.964, compound 5 ≤ 2%). The mixture was filtered and water (28 Kgs) and ethyl acetate (8.9 Kgs) were added to the filtrate. The pH was adjusted to 8 - 9 using 6N HCl then stirred for up to 3 hours before filtering. The filter cake was washed with cold water (25.7 Kgs), then dried under reduced pressure to constant weight. The crude solid compound (I) was determined to be Form IV/ Pattern D.

The crude solid (1.87 Kgs) was suspended in isopropyl alcohol (IPA, 27.1 Kg). The slurry was heated to 75±5 °C to dissolve the solids. The solution was seeded with crystals of Compund (I) (Form I/Pattern A), and was allowed to cool to ambient temperature. The resulting precipitate was stirred for 1-2 hours before filtering. The filter cake was rinsed with IPA (2 x 9.5 Kgs), then dried at 45-55°C to constant weight under reduced pressure to result in 1.86 kg crystalline white solid Compound (I) (Form I/Pattern A) in 85% yield and 99.5% purity. See ^{1}HNMR data in Figure 6.

Example 5: Alternative synthesis of Compound (I)

Reaction Scheme



Step (1)

Synthesis of Compound 11: Ethyl 2-chloropyrimidine-5-carboxylate (ACY-5, 250g), ethanol (2179 g), 2-Chloroaniline (339.3 g, 2 eq) and acetic acid (132.1 g, 1.6 eq) were charged to a reactor under inert atmosphere. The mixture was heated to reflux. After at least 5 hours the reaction was sampled for HPLC analysis. When analysis indicated reaction completion (< 1% ACY-5), the mixture was cooled to 70 ± 5 °C and N,N-Diisopropylethylamine (DIPEA, 553.6 g, 3.2 eq) was added. The reaction was then cooled to 20 ± 5°C and the mixture was stirred for an additional 2-6 hours. The resulting precipitate is filtered and washed with ethanol (2 x 401 g) and heptane (2 x 428 g). The cake is dried under reduced pressure at 50 ± 5 °C to a constant weight to produce 307.1g compound 11 (82.5% yield and 99.7% purity.

Step (2)

Synthesis of Compound 3: Cuprous iodide (17.5g, 8 eq), potassium carbonate (373.8 g, 3 eq), L-Prolin (11.4 g, 0.11 eq.) and dimethyl sulfoxide (DMSO, and 1180 g) were added to a reactor (vessel A). The resulting solution was heated to 90 ± 5°C. In a separate reactor (vessel B), a solution of compound 11 (250g) and iodobenzene (1469.5 g, 8 eq) in DMSO (402.5 g) was heated at 40 ± 5°C. The mixture was then transferred to vessel A over 2-3 hours. The reaction mixture was heated at 90 ± 5°C for 8-24 hours, until HPLC analysis determined that ≤ 1% compound 11 was remaining.

Step (3)

Synthesis of Compound 4: The mixture of Step (2) was cooled to 40-50 °C and water (500g) and potassium hydroxide solution 10% (700.0 g, 2.8 eq) were added. The reaction mixture was stirred at 40-50 °C for 2-8 hours until HPLC showed that ≤1% compound 3 was remaining. The reactor was cooled to 25 °C. The reaction mixture was filtered through Celite, then a 0.2 micron filter, and the filtrate was collected. The filtrate was extracted with toluene (3 x 150g). The aqueous layer was cooled to 0-5 °C, then acidified with hydrochloric acid (HCl) to pH 2-3 while keeping the temperature < 25°C. The reaction was then cooled to 5-15 °C. The precipitate was filtered and washed with cold water. The cake was dried at 45-55 °C under reduced pressure to constant weight to obtain 291 g (81% yield) compound 4 in 98% AUC purity. No dechlorinated product or Cl-migration product (i.e., de-Cl-4 or m-Cl-4) was observed.

Step (4)

Synthesis of Compound 5:

Compound **4** (250.0 g), A-1 (159.2 g, 1.06 eq) and Methy-THF (5113 g) were charged to the reactor. DIPEA (283.7 g, 2.85 eq), hydroxybenzotriazole (HOBt, 12.5 g, 0.11 eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC.HCl, 216.3 g, 1.47 eq) were added. The reaction solution was stirred at ambient temperature for 6-24 hours, at which point HPLC analysis indicated reaction completion (compound 4 ≤3%). The mixture was then extracted with a 1M HCl solution (2270 g), purified water (2270 g), 7% sodium bicarbonate (2270 g), purified water (2270 g), and 25% sodium chloride solution (2270 g). The Methyl-THF was then vacuumdistilled at < 40 °C and chased repeatedly with isopropyl alcohol. When analysis indicated that <1 mol% methyl-THF was remaining, the mixture was gradually cooled to 0-5 °C and was stirred at 0-5 °C for an at least 2 hours. The resulting precipitate was collected by filtration and washed with cold isopropyl alcohol (700g). The cake was sucked dry on the filter for 4-24 hours, then was further dried at 45-55 °C under reduced pressure to constant weight. 294g (82% yield) was isolated in 99.6% AUC purity and 99.4 wt %.

Step (5)

Synthesis of Compound (I): Hydroxylamine hydrochloride (330g, 10 eq) and methanol (960g) were charged to a reactor. The resulting solution was cooled to 0-5 °C and 25% sodium methoxide (1120 g, 11 eq) was charged slowly, maintaining the temperature at 0-10 °C. Once

the addition was complete, the reaction was mixed at 20 °C for 1-3 hours and filtered, and the filter cake was washed with methanol (2 x 210 g). The filtrate (hydroxylamine free base) was returned to the reactor and cooled to 0±5°C. Compound 5 (220 g) was added. The reaction was stirred until the reaction was complete (compound 5 ≤ 2%). The mixture was filtered and water (280 g) and ethyl acetate (890 g) were added to the filtrate. The pH was adjusted to 8 - 9 using HCl then stirred for up to 3 hours before filtering. The filter cake was washed with cold water (2570 g), then dried under reduced pressure to constant weight to yield 980 g crude solid in 83% yield. The crude solid compound (I) was determined to be Form IV/ Pattern D.

The crude solid (980 g) was suspended in 1-propanol (400 g) and purified water (220 g). The suspension was heated to 40°C. The batch was then cooled to 38°C over 30 minutes. The solution was seeded with crystals of Compund (I) (Form I/Pattern A, 2-5 wt %). The batch was kept at 37-38°C for 2-4 hours, then was gradually cooled to 20±2°C. Water (950 g) was charged over 3 -5 hours. The batch was cooled to 12°C and was stirred for 2 hrs at this temperature. The batch was filtered and washed with cold 1-propanol/water, then dried at 50±5°C to constant weight to yield 910 g purified compound (I) in 93% yield and 99.8% AUC purity.

HPLC Methods

I. Method 113.1016

Column	Zorbax Eclipse XDB-C18, 4.6 mm x 150 mm, 3.5 μm		
Column Temperature	40ºC		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 215 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 μL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	40.0 min		
Run Time	46.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	36.0	0%	100%
	40.0	0%	100%
	40.1	98%	2%
	46.0	98%	2%

II. Method 113.942

Column	ACE Excel 3 super C18, 4.6 mm x 150 mm, 3 μm		
Column Temperature	40ºC		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 214 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 μL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	22.0 min		
Run Time	28.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	18.0	0%	100%
	22.0	0%	100%
	22.1	98%	2%
	28.0	98%	2%

III. Method 113.953

Column	ACE Excel 3 super C18, 4.6 mm x 150 mm, 3 μm		
Column Temperature	40ºC		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 235 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 μL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	40.0 min		
Run Time	46.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	36.0	0%	100%
	40.0	0%	100%
	40.1	98%	2%
	46.0	98%	2%

5

IV. Method 113.946

Column	Zorbax Eclipse XDB-C18, 4.6 mm x 150 mm, 3.5 µm		
Column Temperature	40ºC		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 214 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 µL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	40.0 min		
Run Time	46.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	36.0	0%	100%
	40.0	0%	100%
	40.1	98%	2%
	46.0	98%	2%

V. Method 113.964

Column	ACE Excel 3 super C18, 4.6 mm x 150 mm, 3 µm		
Column Temperature	40ºC		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 272 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 µL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	40.0 min		
Run Time	46.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	36.0	0%	100%
	40.0	0%	100%
	40.1	98%	2%
	46.0	98%	2%

5

VI. Method 113.941

Column	Zorbax Eclipse XDB-C18, 4.6 mm x 150 mm, 3.5 µm		
Column Temperature	40°C		
UV Detection Wavelength	Bandwidth 4 nm, Reference off, 272 nm		
Flow rate	1.0 mL/min		
Injection Volume	10 µL with needle wash		
Mobile Phase A	0.05% trifluoroacetic acid (TFA) in purified water		
Mobile Phase B	0.04% TFA in acetonitrile		
Data Collection	40.0 min		
Run Time	46.0 min		
Gradient	Time (min)	Mobile Phase A	Mobile Phase B
	0.0	98%	2%
	36.0	0%	100%
	40.0	0%	100%
	40.1	98%	2%
	46.0	98%	2%

Crystal Forms of Compound (I)

I. *Form I/ Pattern A*

2-((2-chlorophenyl)(phenyl)amino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide (i.e., compound (I)) may exist in crystal Form I (referred to herein as "Form I"). Form I can be characterized using X-ray powder diffraction (XRPD). The XRPD pattern of Form I is shown in Figure 8, and is refered to as "Pattern A".

Table 5. Peak list for Pattern A (Figure 8)

Angle (2Θ) degree	**Intensity %**	**d value (Å)**
8.31	100	10.626
10.00	15.3	8.834
10.62	17.8	8.327
12.82	6.4	6.898
15.62	9.2	5.667
16.60	36.4	5.337
17.20	9.4	5.152
17.67	9.5	5.014
19.63	8.5	4.518

19.99	22.7	4.438
20.64	10.1	4.300
21.08	18.2	4.210
21.33	32.4	4.162
24.41	7.3	3.643
24.95	30.7	3.566
26.08	16.1	3.413

Form I can also be characterized by differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) (see Figures 8 and 9, respectively). The dynamic vapor sorption (DVS) experiment revealed less than 0.2 % of moisture uptake by Compound (I), Form I/ Pattern A, when subjected to relative humidity between 0-95 percent and no change in the crystalline form was observed. DSC analysis also indicated an endothermic thermal event (melting point) at around 173 °C, followed by an exothermic event (possible decomposition). TGA analysis revealed that there is less than 0.1% weight loss in the sample from 35 to 150 °C.

Karl Fischer (KF) titration also revealed less than < 1 % of water content.

Form I of compound (I) can be prepared from amorphous compound (I), or from another crystalline form of compound (I), by stirring for 8-16 hours (e.g., overnight) in a slurry of ethanol.

II. *Form IV/Pattern D*

2-((2-chlorophenyl)(phenyl)amino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide (i.e., compound (I)) may exist in crystal Form IV (referred to herein as "Form IV"). Form IV can be characterized using X-ray powder diffraction (XRPD). The XRPD pattern of Form IV is shown in Figure 11, and is refered to as "Pattern D".

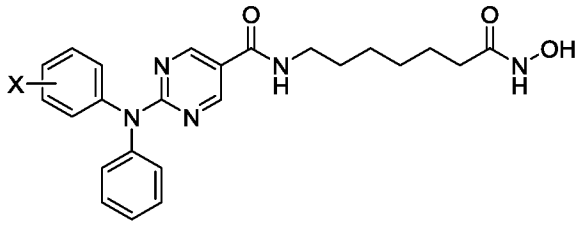
Table 6. Peak list for Pattern D XRPD, Form IV

Angle (2Θ) degree	Intensity %	d value (Å)
5.13	32.9	17.212
11.78	100	7.508
13.60	61.8	6.506
13.80	77.2	6.412
14.48	10.4	6.112

16.01	15	5.532
17.13	19.9	5.172
20.30	26.7	4.370
21.16	10.6	4.195
23.69	82.4	3.753
24.05	42.7	3.698
24.70	13.3	3.601
25.16	25.1	3.536
26.95	19	3.306
27.36	14.3	3.258
30.61	9.1	2.918

CLAIMS

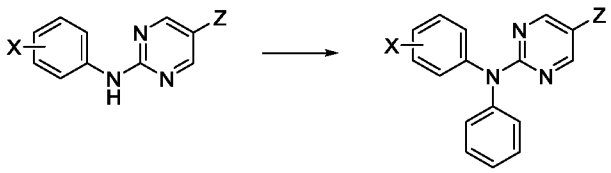
1. A method of making compound (Ia):



(Ia)

comprising the steps of:

converting compound 11a into compound 3a:



11a 3a ;

wherein X is selected from fluorine, chlorine, bromine and iodine;

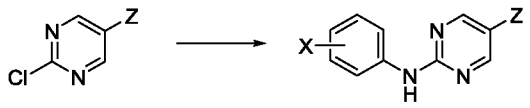
Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl; and

converting compound 3a into compound (Ia).

2. The method of claim 1, wherein compound 11a is prepared by a method comprising the step of:

converting compound 1a into compound 11a:



1a 11a ;

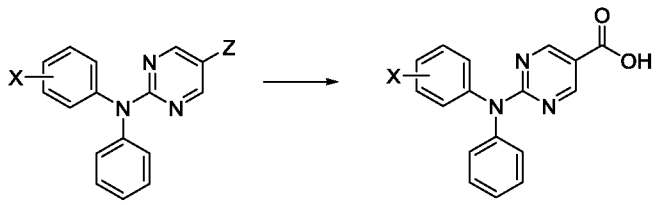
wherein X is selected from fluorine, chlorine, bromine and iodine;

Z is selected from the group consisting of –CN and $–CO_2R$; and

R is C_1-C_6 alkyl.

3. The method of claim 1, wherein the step of converting compound 3a into compound (Ia) comprises the steps of:

converting compound 3a into compound 4a:

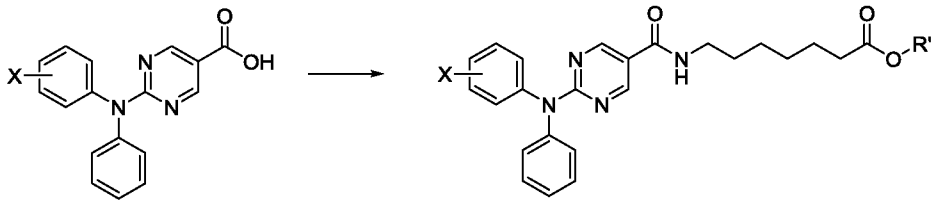


3a 4a ; and

converting compound 4a into compound (Ia).

4. The method of claim 3, wherein the step of converting compound 4a into compound (Ia) comprises the steps of:

converting compound 4a into compound 5a:

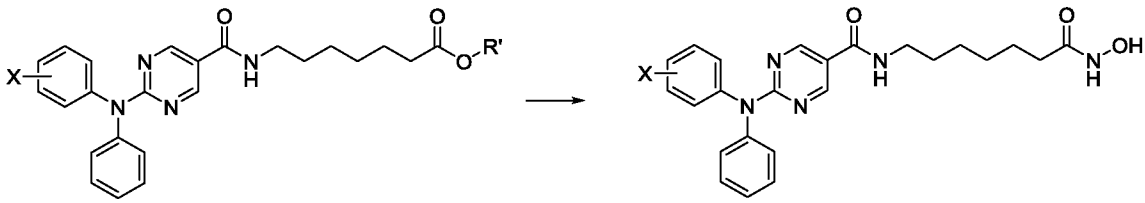


4a 5a ;

wherein X is selected from fluorine, chlorine, bromine and iodine; and

R' is C_1-C_6 alkyl; and

converting compound 5a into compound (Ia):



5a (Ia)

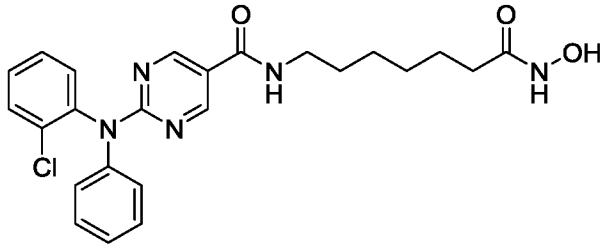
wherein X is selected from fluorine, chlorine, bromine and iodine.

5. The method of any one of claims 1-4, wherein X is chlorine.

6. The method of any one of claims 1-5, wherein Z is CO_2Et.

7. The method of any one of claims 4-6, wherein R' is methyl.

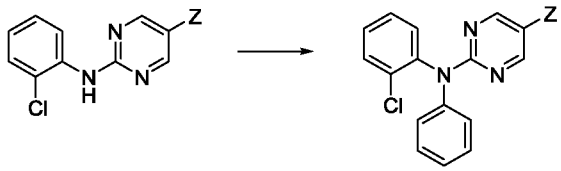
8. A method of making compound (I):



(I)

comprising the steps of:

converting compound 11b into compound 3b:



11b 3b ;

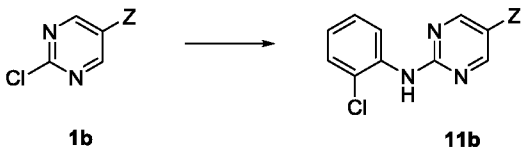
wherein Z is selected from the group consisting of –CN and $–CO_2R$;

wherein R is C_1-C_6 alkyl; and

converting compound 3b into compound (I).

9. The method of claim 8, wherein compound 11b is prepared by a method comprising the step of:

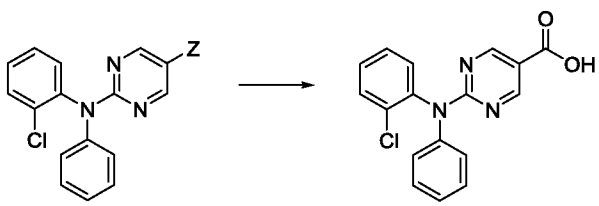
converting compound 1b into compound 11b:



1b 11b .

10. The method of claim 8, wherein the step of converting compound 3b into compound (I) comprises:

converting compound 3b into compound 4:

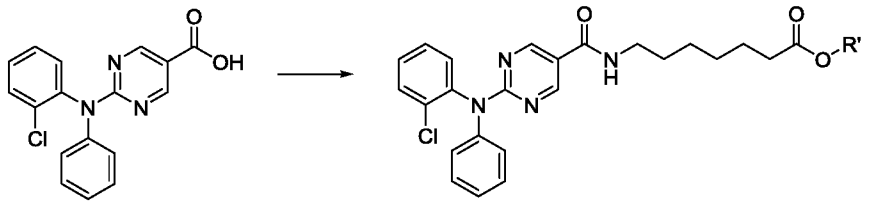


3b 4 ; and

converting compound 4 into compound (I).

11. The method of claim 10, wherein the step of converting compound 4 into compound (I) comprises:

converting compound 4 into compound 5b:



4 5b ;

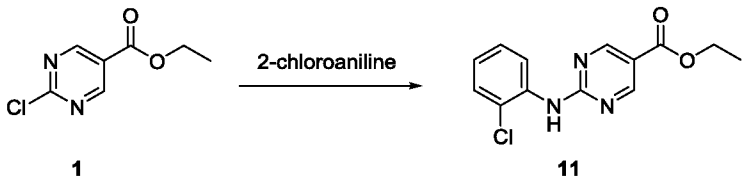
wherein R' is C_1-C_6 alkyl; and

converting compound 5b into compound (I).

12. The method of any one of claims 8-10, wherein Z is CO_2Et.

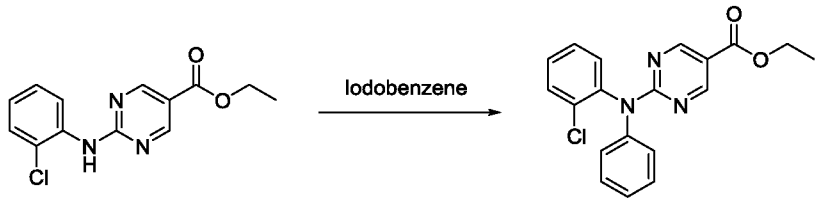
13. The method of claim 11, wherein R' is methyl.

14. The method of any one of claims 9-13, wherein the step of converting compound 1b into compound 11b comprises reacting compound 1 with 2-chloroaniline to obtain compound 11:



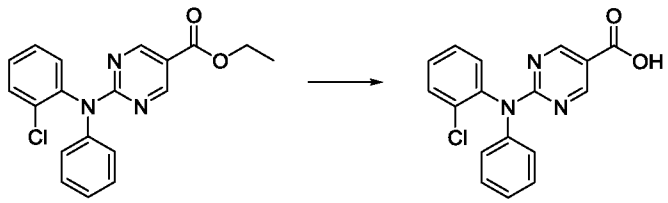
1 11 .

15. The method of any one of claims 8-14, wherein the step of converting compound 11b into compound 3b comprises reacting compound 11 with iodobenzene to obtain compound 3:



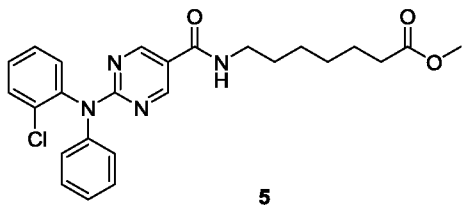
11 3 .

16. The method of any one of claims 10-15, wherein the step of converting compound 3b into compound 4 comprises comprises hydrolyzing the ester of compound 3:



3 4

17. The method of any one of claims 11-16, wherein the step of converting compound 4 into compound 5b comprises reacting compound 4 with methyl 7-aminoheptanoate to obtain compound 5:

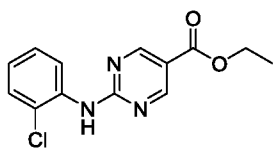


5

18. The method of any one of claims, wherein the step of converting compound 5b into compound (I) comprises reacting compound 5 with hydroxylamine, or a salt thereof, to obtain compound (I), or a salt thereof.

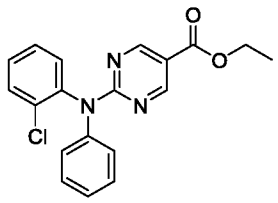
19. A method of making compound (I) comprising the following steps:

(1) reacting ethyl 2-chloropyrimidine-5-carboxylate with 2-chloroaniline to obtain compound 11:



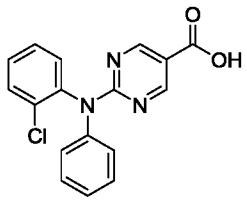
11 ;

(2) reacting compound 11 with iodobenzene to obtain compound 3:



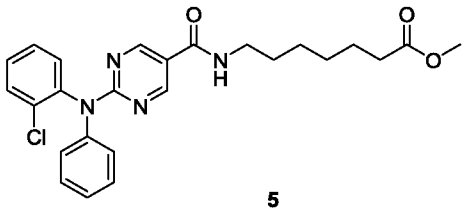
3 ;

(3) reacting compound 3 with aqueous base, followed by reacting with acid, to obtain compound 4:



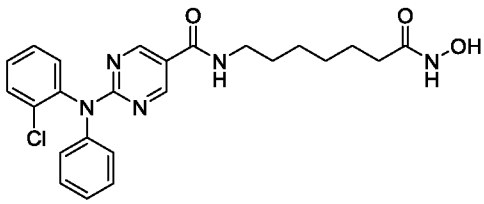
4 ;

(4) reacting compound 4 with methyl 7-aminoheptanoate to obtain compound 5:



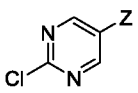
5 ; and

(5) reacting compound 5 with hydroxylamine, or a salt thereof, to obtain compound (I), or a salt thereof:



(I) .

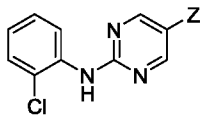
20. A composition comprising:



G1 ;

wherein Z is selected from the group consisting of –CN and $–CO_2R$; and

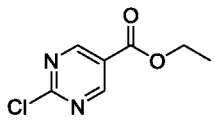
wherein R is C_1-C_6 alkyl; and



G11 :

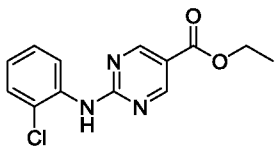
wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl.

21. The composition of claim 20, wherein 1b is compound 1:



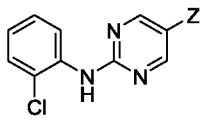
1 ; and

wherein 11b is compound 11:



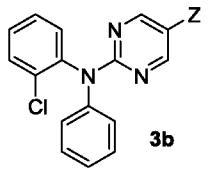
11 .

22. A composition comprising:



11b ;

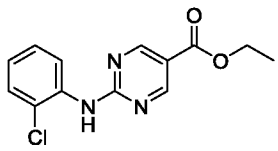
wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl; and



3b :

wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl.

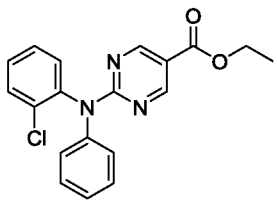
23. The composition of claim 22, wherein 11b is compound 11:



11

; and

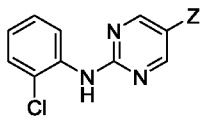
wherein 3b is compound 3:



3

.

24. A compound having the structure of 11b:



11b

:

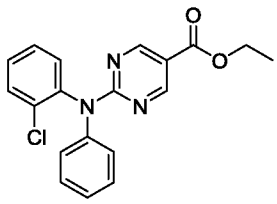
wherein Z is selected from the group consisting of –CN and $–CO_2R$; and wherein R is C_1-C_6 alkyl.

25. The compound of claim 24, wherein Z is $–CO_2R$.

26. The compound of claim 25, wherein R is ethyl.

27. A composition comprising the compound of claim 24.

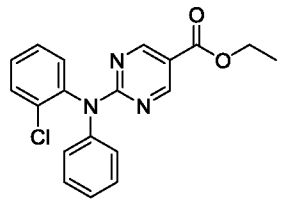
28. The composition of claim 27, further comprising compound 3:



3

.

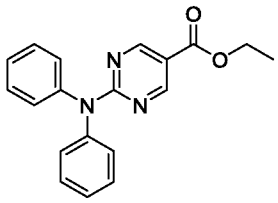
29. A composition comprising compound 3:



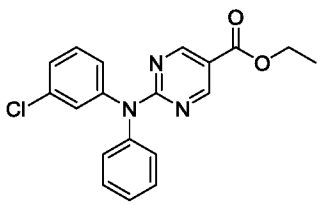
3

,

wherein the composition is free from compounds de-Cl-3 and m-Cl-3:



de-Cl-3

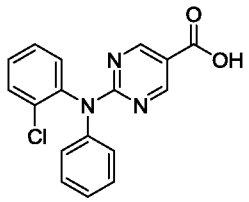


m-Cl-3

.

5

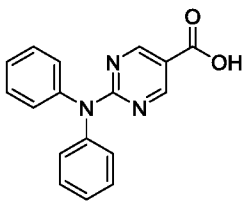
30. A composition comprising compound 4:



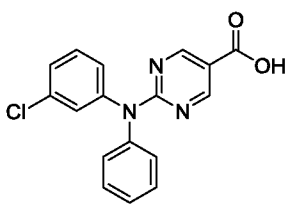
4

,

wherein the composition is free from compounds de-Cl-4 and m-Cl-4:



de-Cl-4

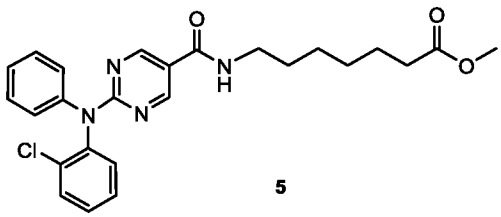


m-Cl-4

.

10

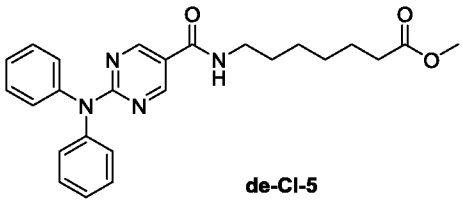
31. A composition comprising compound 5:



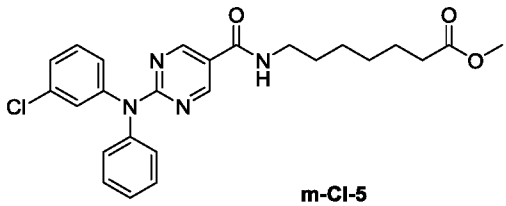
5

,

wherein the composition is free from compounds de-Cl-5 and m-Cl-5:



de-Cl-5



m-Cl-5

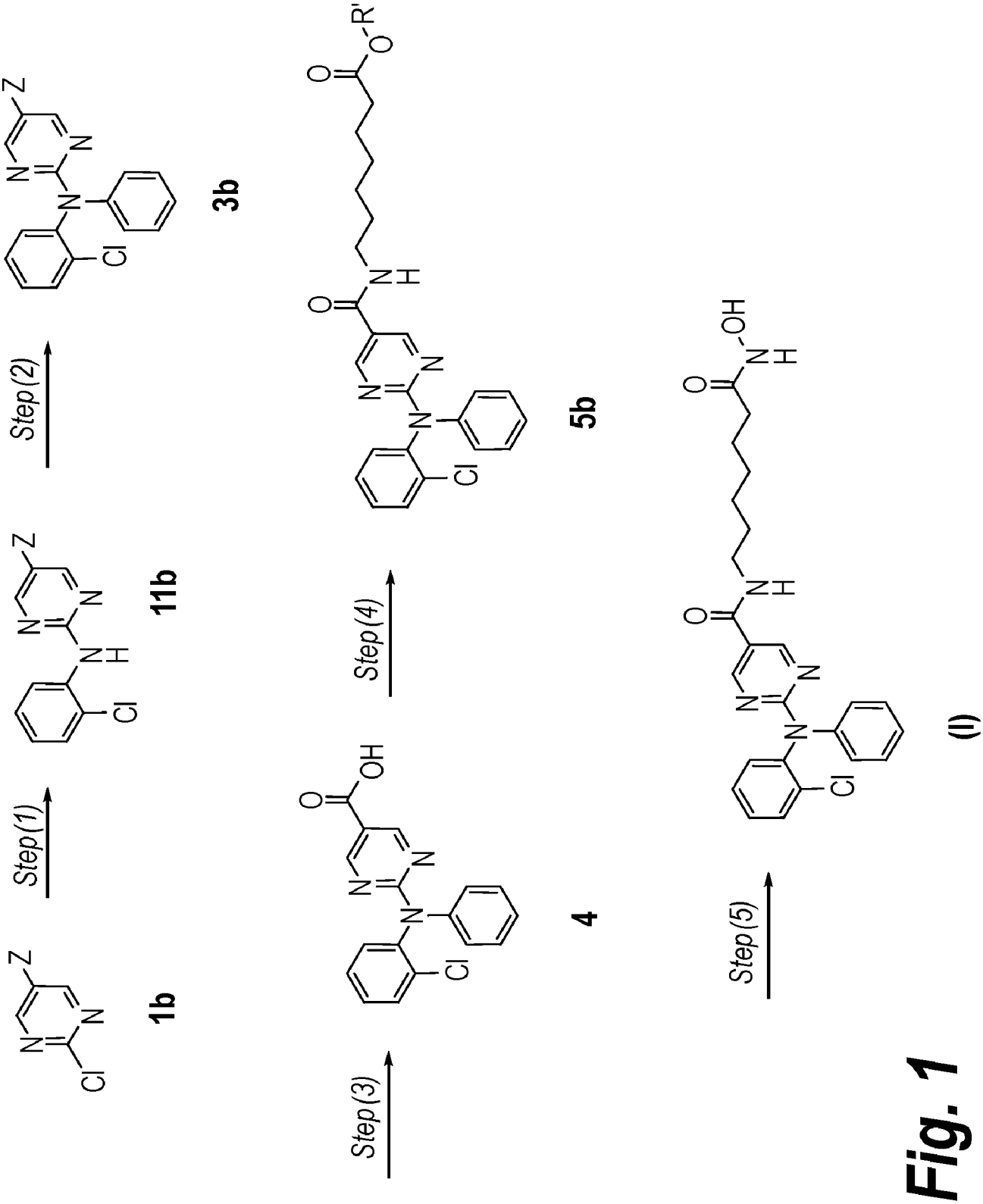

Z
N
N
Cl
1b
Step (1)
Z
N
N
NH
Cl
11b
Step (2)
Z
N
N
N
Cl
3b
O
O-R'
NH
O
N
N
N
Cl
5b
Step (3)
O
OH
N
N
N
Cl
4
Step (4)
O
NH
OH
N
N
N
Cl
(I)
Step (5)

Fig. 1

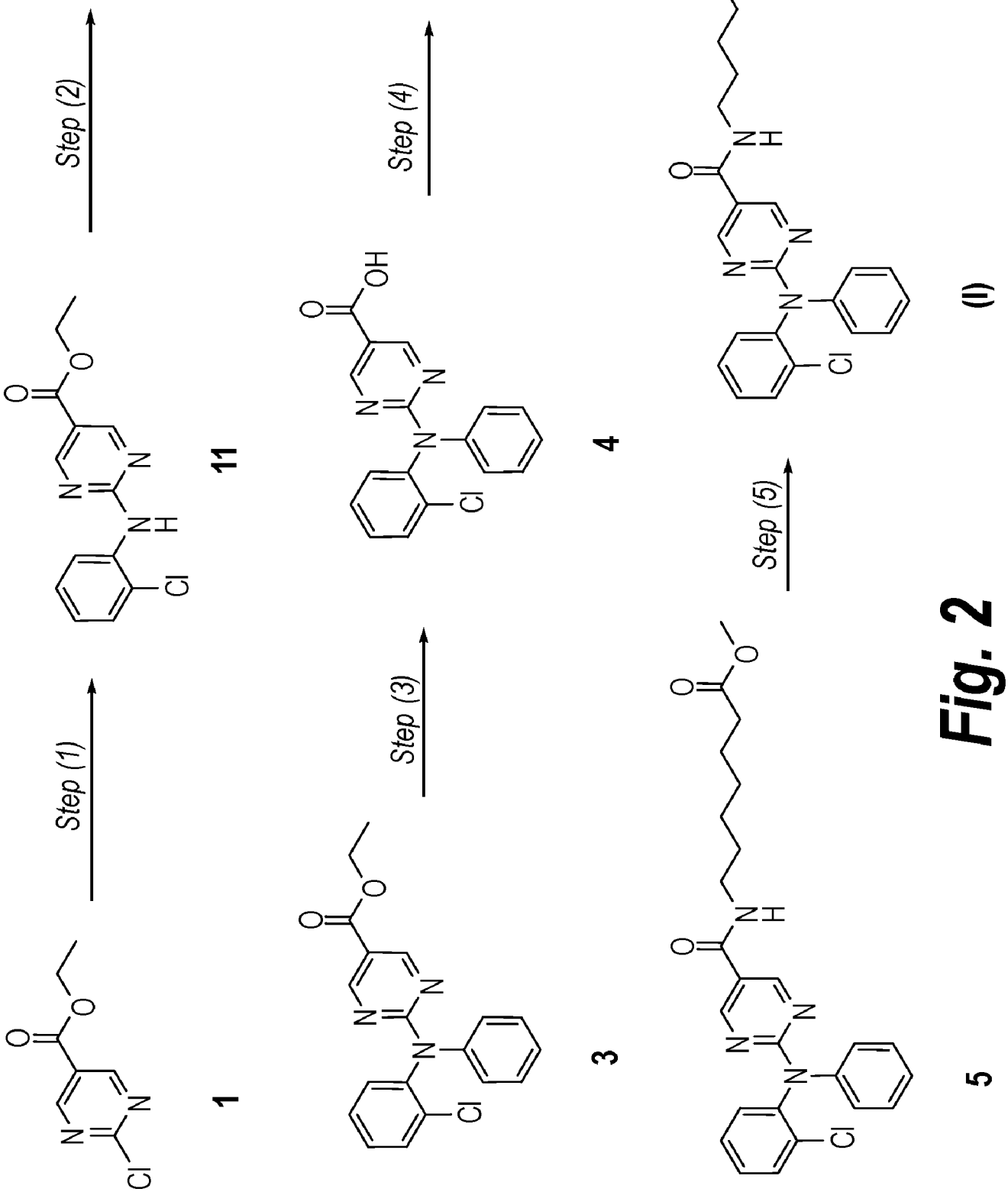
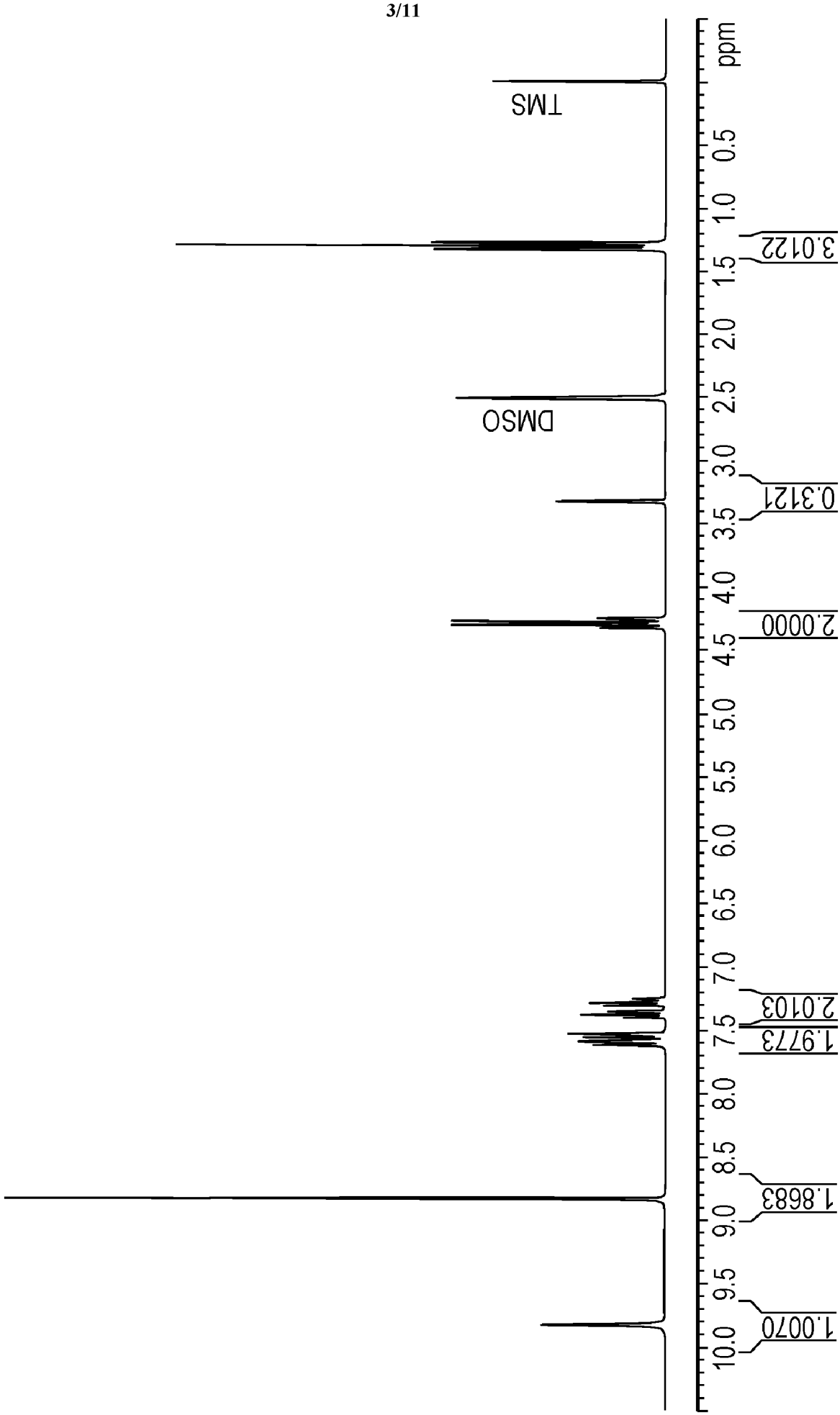


Fig. 2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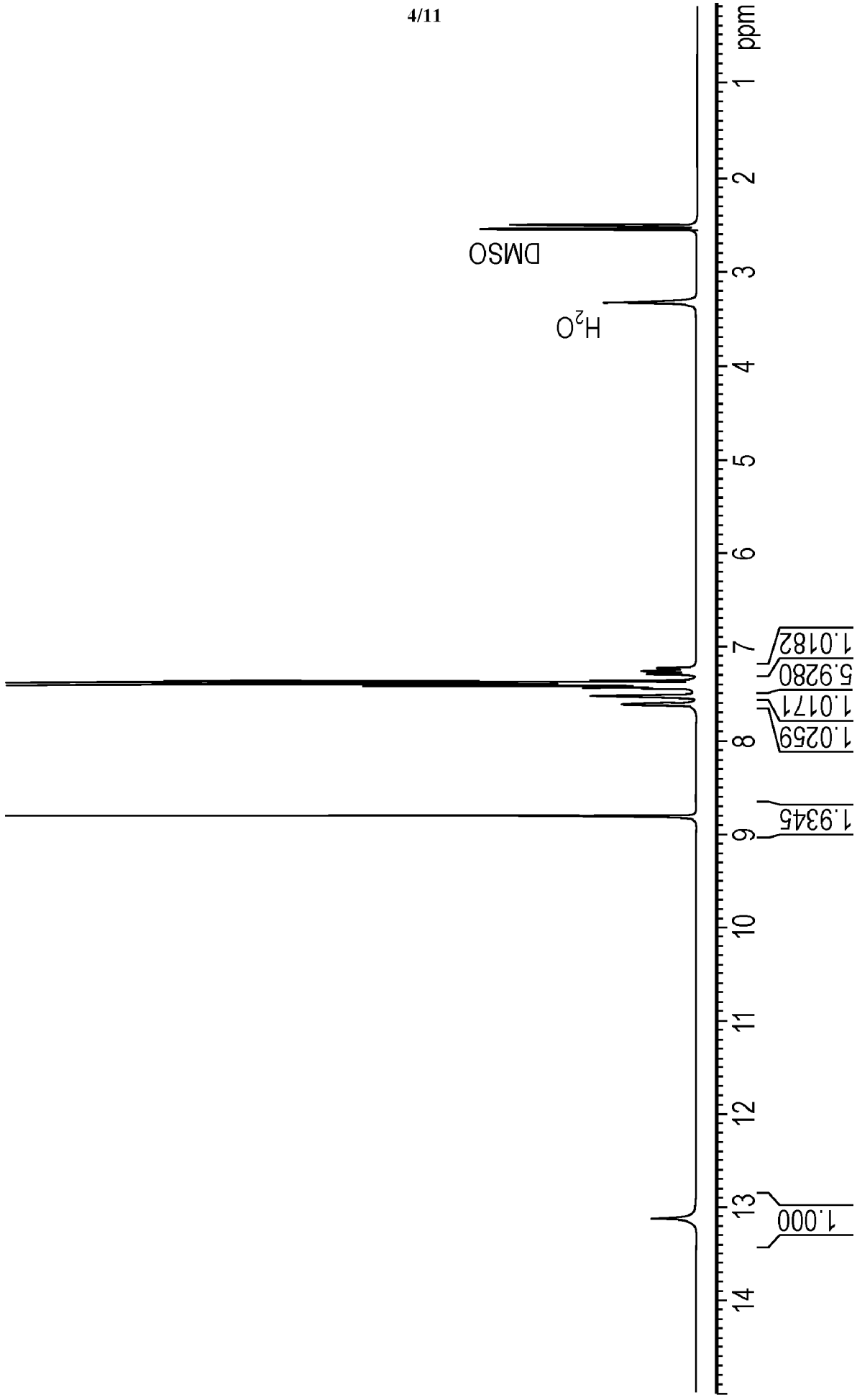
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
3.0122
0.3121
2.0000
2.0103
1.9773
1.8683
1.0070

Fig. 3


DMSO
H2O
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5.9280
1.0171
1.0259
1.9345
1.000
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
14

Fig. 4

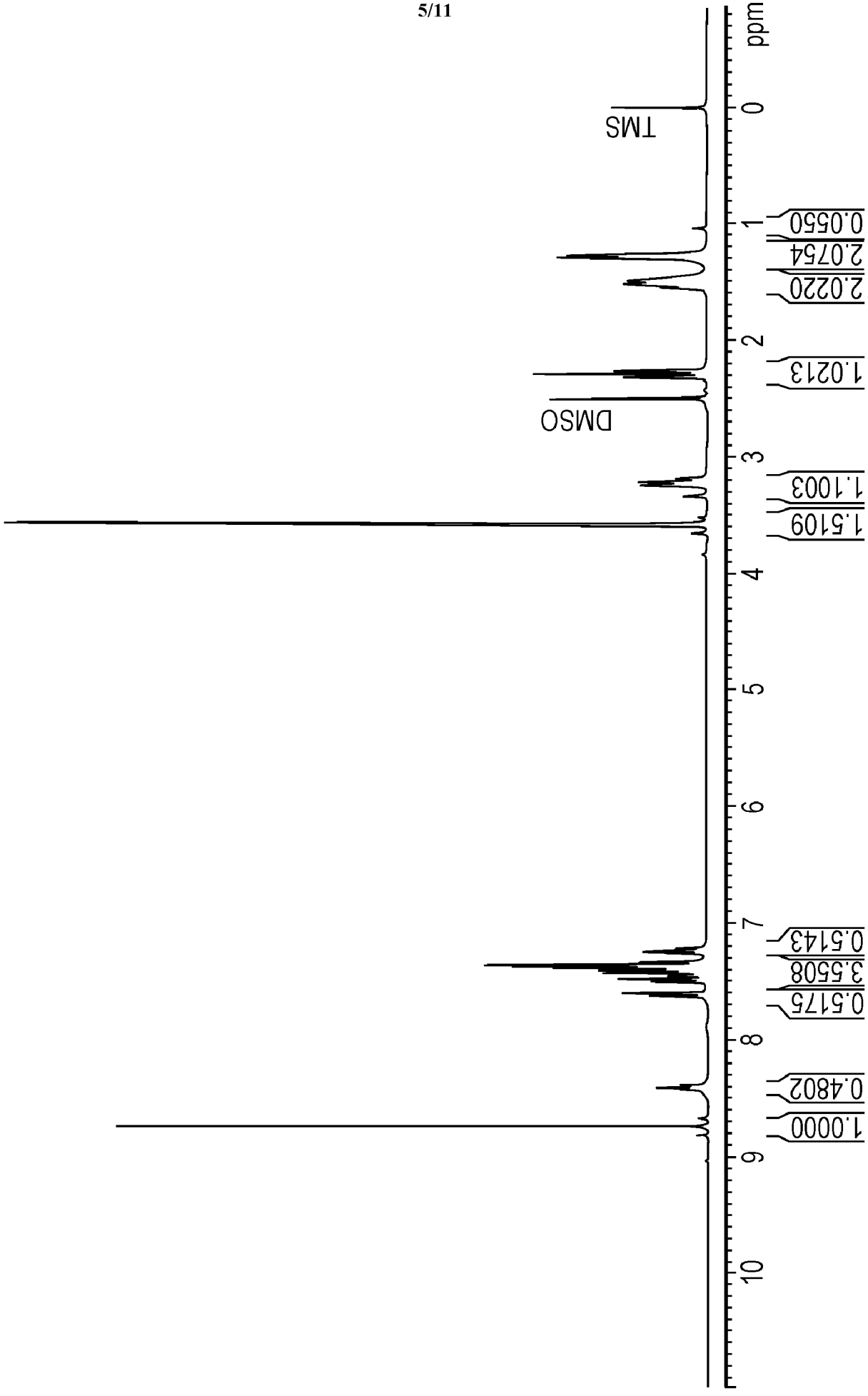

TMS
DMSO
ppm
0
1
2
3
4
5
6
7
8
9
10
0.0550
2.0754
2.0220
1.0213
1.1003
1.5109
0.5143
3.5508
0.5175
0.4802
1.0000

Fig. 5

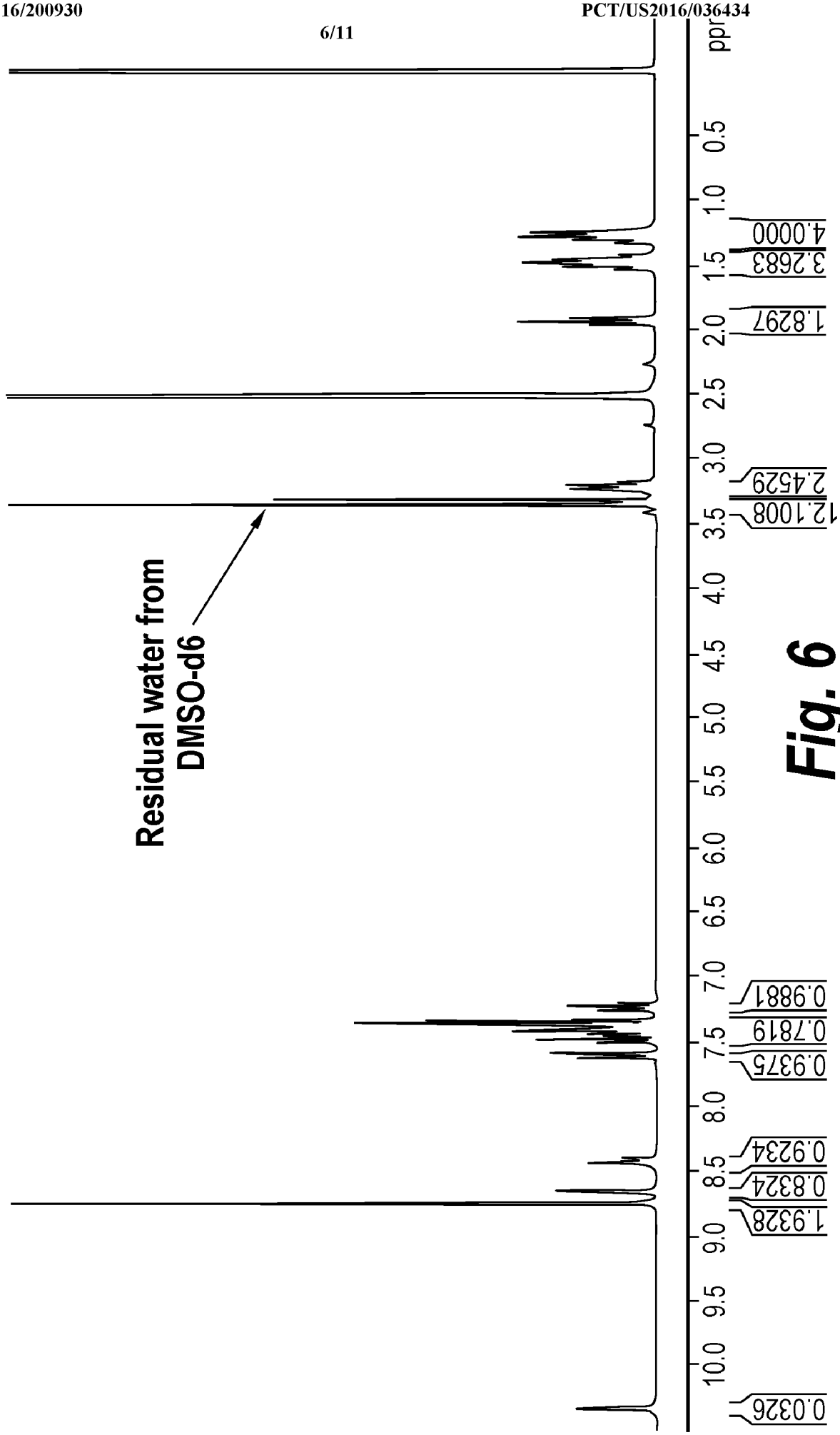
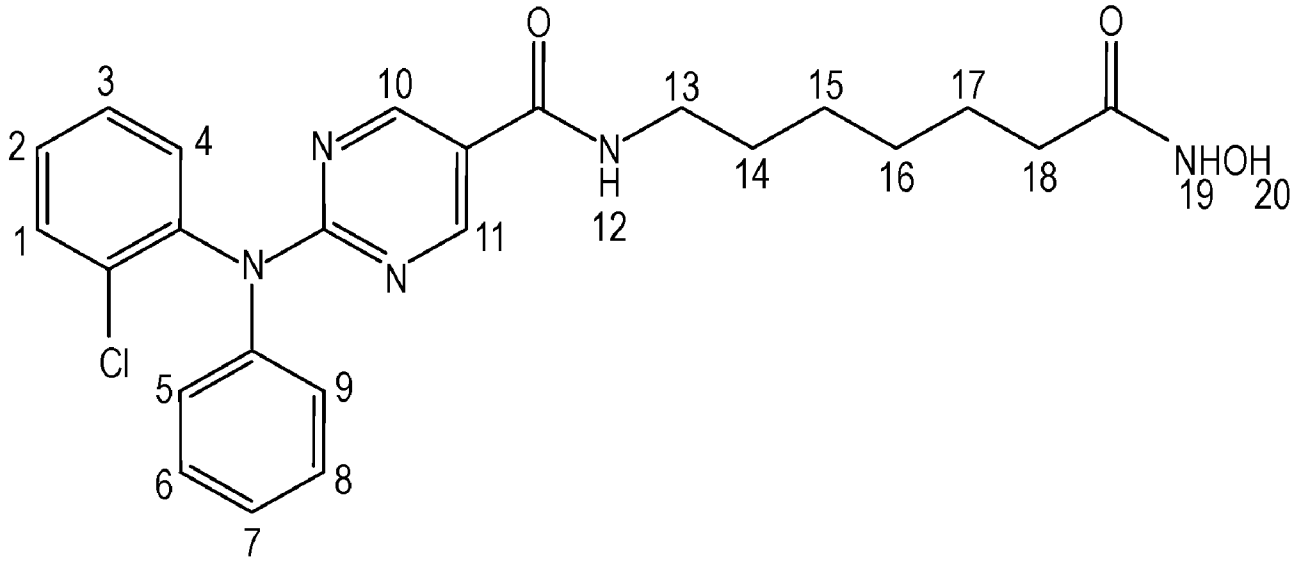
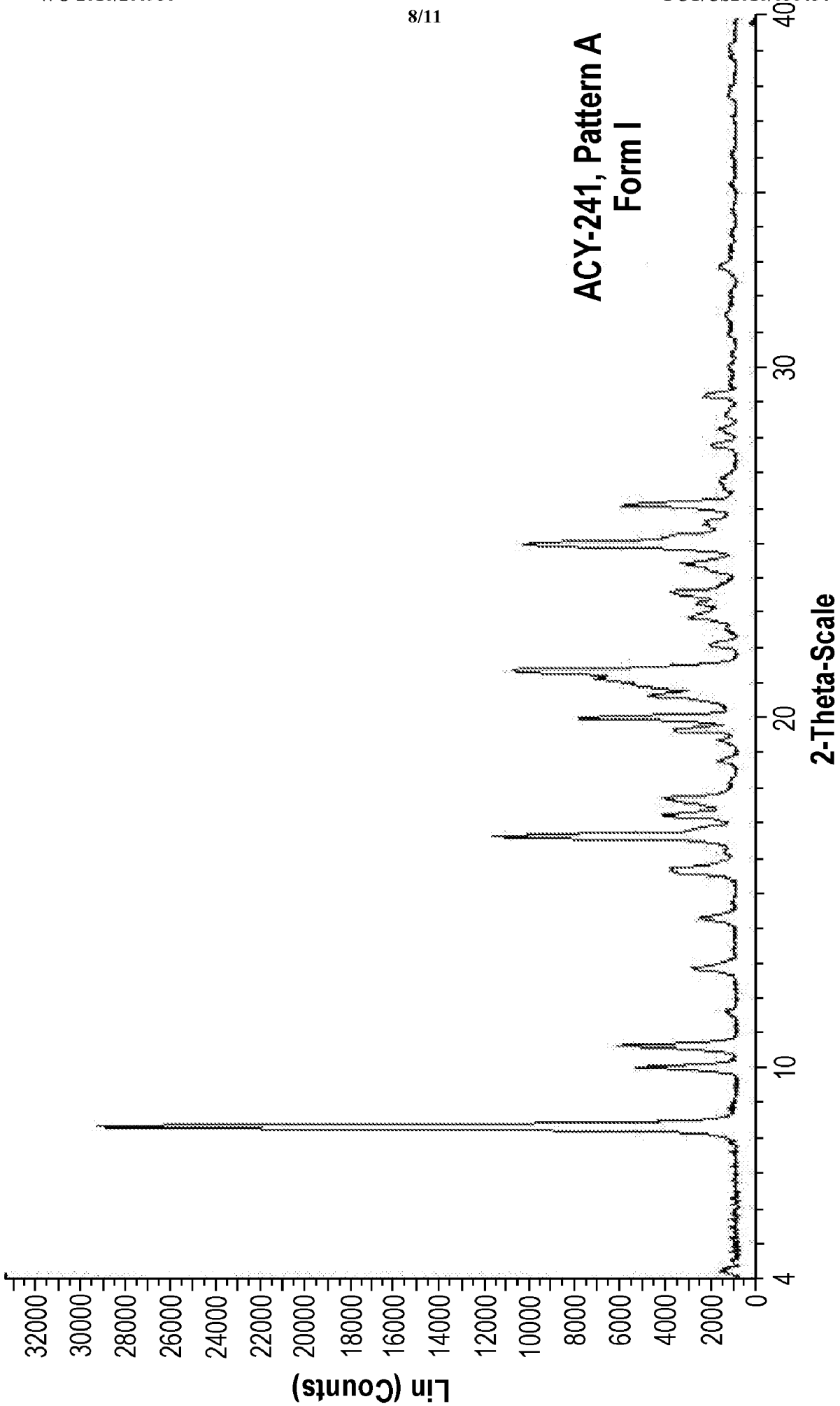

Residual water from DMSO-d6
ppm
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0326
1.9328
0.8324
0.9234
0.9375
0.7819
0.9881
12.1008
2.4529
1.8297
3.2683
4.0000

Fig. 6



^{1}H Signal Peak, ppm	Assigned Proton (Figure 1)
10.35 (1H, s)	19
8.76 (2H, s)	10, 11
8.67 (1H, s)	20
8.42 (1H, t, J=4.4Hz)	12
7.62 (1H, dd, J1=7.6Hz, J2=2.0Hz)	1
7.52 (1H, dd, J1 = 7.6 Hz, J2=2.0Hz) 7.42 (6H, m, J=6.0Hz)	4 2,3, 5, 6, 8, 9,
7.21 (1H, tt, J1=7.2Hz, J2=1.6Hz)	7
3.24 (2H, q)	13
1.97 (2H, t, J=7.2Hz)	18
1.49 (4H, m)	14, 17
1.26 (4H, m)	15, 16

Fig. 7


ACY-241, Pattern A
Form I
Lin (Counts)
2-Theta-Scale
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30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
4
10
20
30
40

Fig. 8

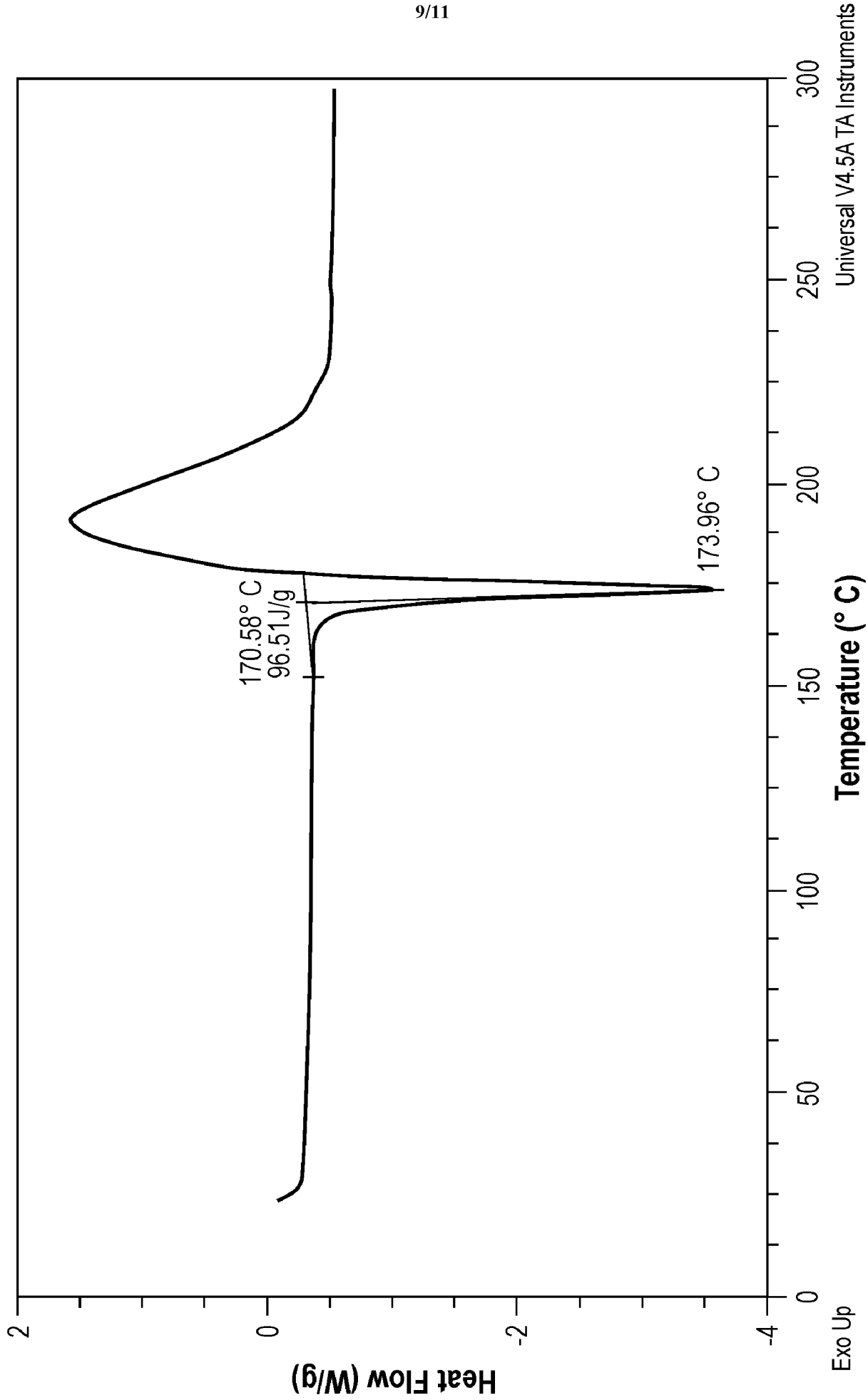
Heat Flow (W/g)
2
0
-2
-4
Exo Up
0
50
100
150
200
250
300
Temperature (° C)
Universal V4.5A TA Instruments
170.58° C
96.51J/g
173.96° C

Fig. 9

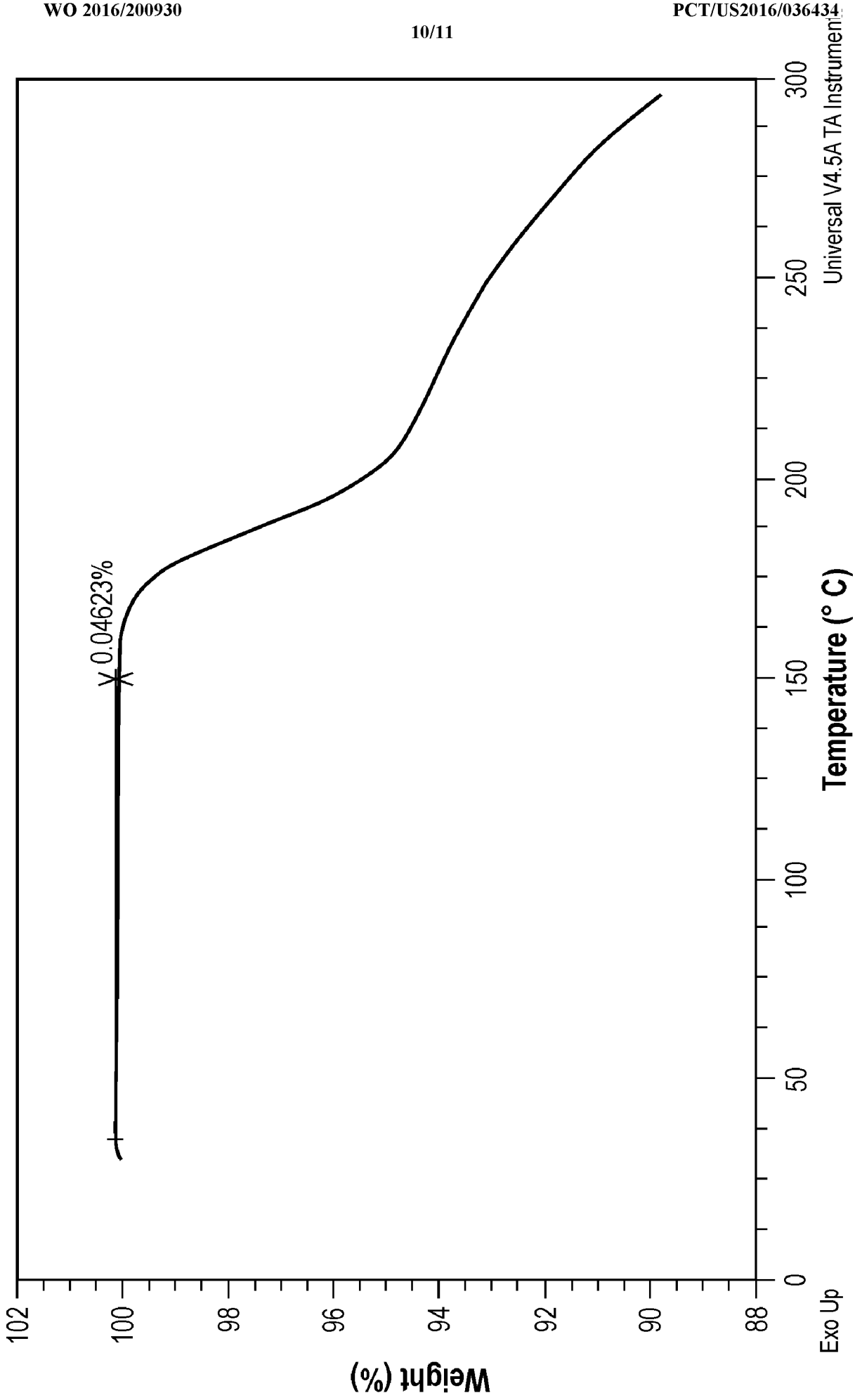
Universal V4.5A TA Instruments
Exo Up
Weight (%)
102
100
98
96
94
92
90
88
0
50
100
150
200
250
300
Temperature (° C)
0.04623%

Fig. 10

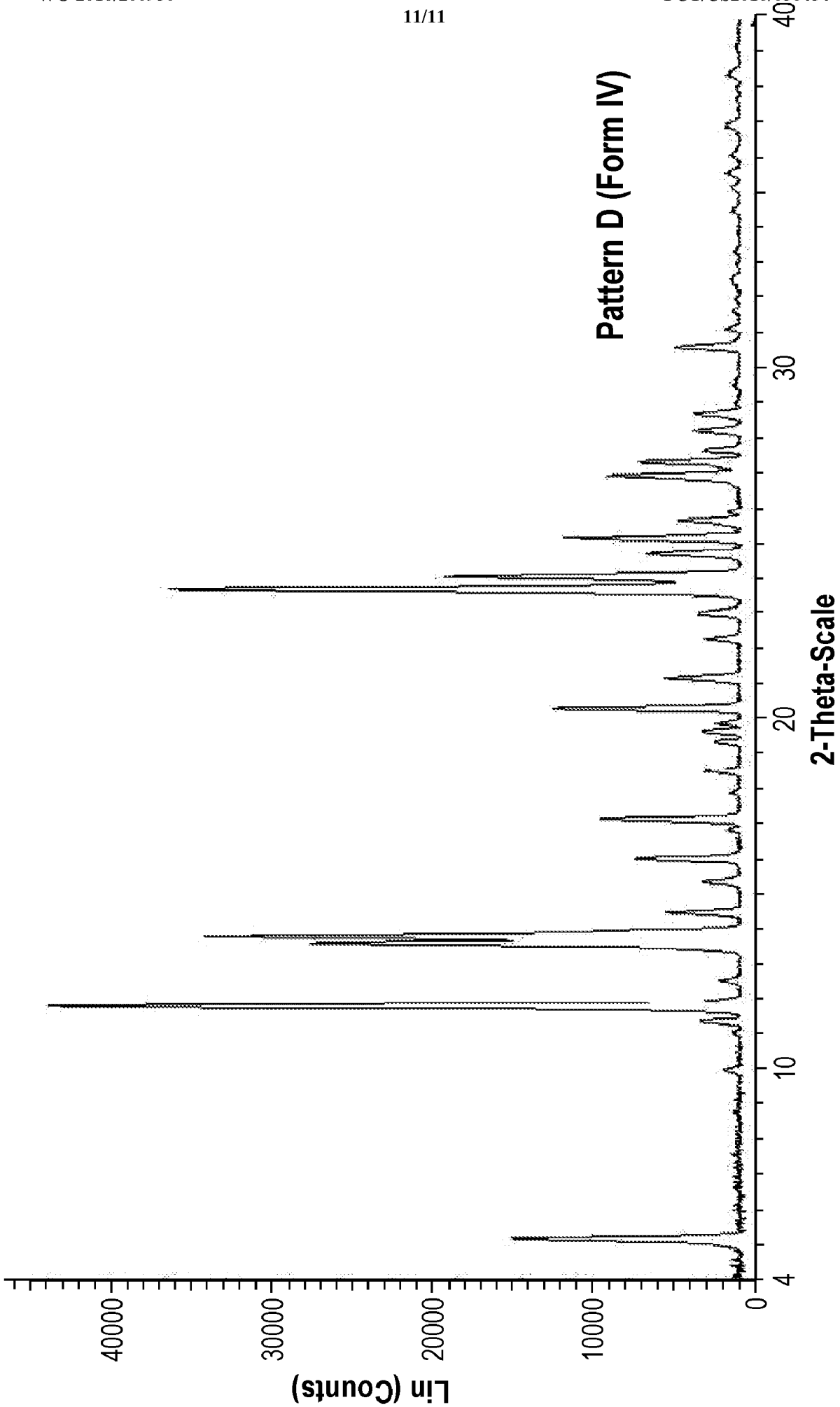
Pattern D (Form IV)
Lin (Counts)
0
10000
20000
30000
40000
4
10
20
30
40
2-Theta-Scale

Fig. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/036434

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/30 C07D239/42
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/054099 A1 (ACETYLON PHARMACEUTICALS INC [US]) 16 April 2015 (2015-04-16)	29-31
Y	page 27 - page 30; examples 2, 1	1-28
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2016	08/08/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VICENTE DEL AMO ET AL: "General Preparation of Primary, Secondary, and Tertiary Aryl Amines by the Oxidative Coupling of Polyfunctional Aryl and Heteroaryl Amidocuprates", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 45, no. 46, 27 November 2006 (2006-11-27), pages 7838-7842, XP055291153, DE ISSN: 1433-7851, DOI: 10.1002/anie.200603089 Page 7840, Table 1, entry 14, preparation of compound 16b	1-28
Y	WO 2013/048949 A2 (SQUIBB BRISTOL MYERS CO [US]) 4 April 2013 (2013-04-04) page 36; example 12	2-7, 9-21, 24-28
Y	SPANKA C ET AL: "Piperidyl amides as novel, potent and orally active mGlu5 receptor antagonists with anxiolytic-like activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 20, no. 1, 1 January 2010 (2010-01-01), pages 184-188, XP026808801, ISSN: 0960-894X [retrieved on 2009-11-05] Table 3 compound 13e, preparation according to scheme 1 method B	2-7, 9-21, 24-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/036434

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