Appeal Decision

Appeal No. 2020-1351

Appellant	TACTICAL THERAPEUTICS, INC.
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Patent Attorney	SUDA, Hiroyuki
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The case of the appeal against the examiner's decision of refusal of Japanese Patent Application No. 2017-150532, entitled "NOVEL COMPOSITIONS AND PROCESSES FOR PREPARING 5-AMINO OR SUBSTITUTED AMINO 1,2,3-TRIAZOLES AND TRIAZOLE OROTATE FORMULATIONS" (the application published on November 16, 2017, Japanese Unexamined Patent Application Publication No. 2017-203038) has resulted in the following appeal decision:

Conclusion

The appeal of the case was groundless.

Reason

No. 1 Brief overview of the history of the procedures

The present application was filed on August 3, 2017 as a divisional application of Japanese Patent Application No. 2015-215891 filed on November 2, which is a divisional application of Japanese Patent Application No. 2012-527868 whose international filing date is September 3, 2010 (claim of priority under the Paris Convention received by the foreign receiving office on September 4, 2009 and September 3, 2010, both in the U.S.A.), and the brief overview of the history of the

procedures after filing the application is as follows:

September 4, 2017 Submission of a written amendment and a written statement
October 11, 2018 Notification of reasons for refusal
April 15, 2019 Submission of a written opinion
September 20, 2019 Decision of refusal
January 31, 2020 Demand for an appeal against examiner's decision of refusal and submission of a written amendment
March 18, 2020 Submission of a written amendment (formality)
September 30, 2020 Submission of a written statement
October 28, 2020 Submission of a written statement

No. 2 Decision to dismiss amendment by the written amendment filed on January 31, 2020

[Conclusion of Decision to Dismiss Amendment]

The amendment by the written amendment filed on January 31, 2020 (hereinafter, referred to as the "Amendment") shall be dismissed.

[Reason]

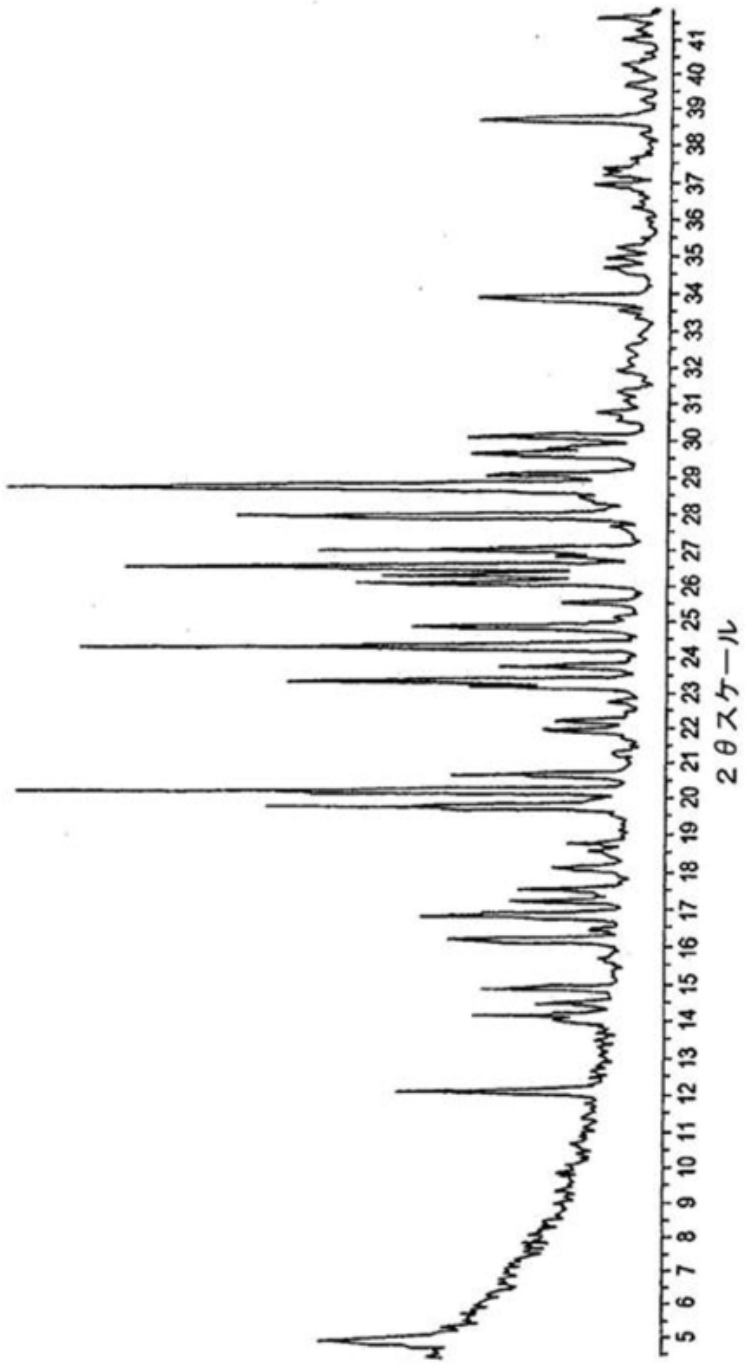
1. Details of the Amendment

The Amendment amends the recitation in Claim 1 of the scope of claims:

"A Form 1 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction pattern substantially shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4.

FIG. 3

[Chemical 1]



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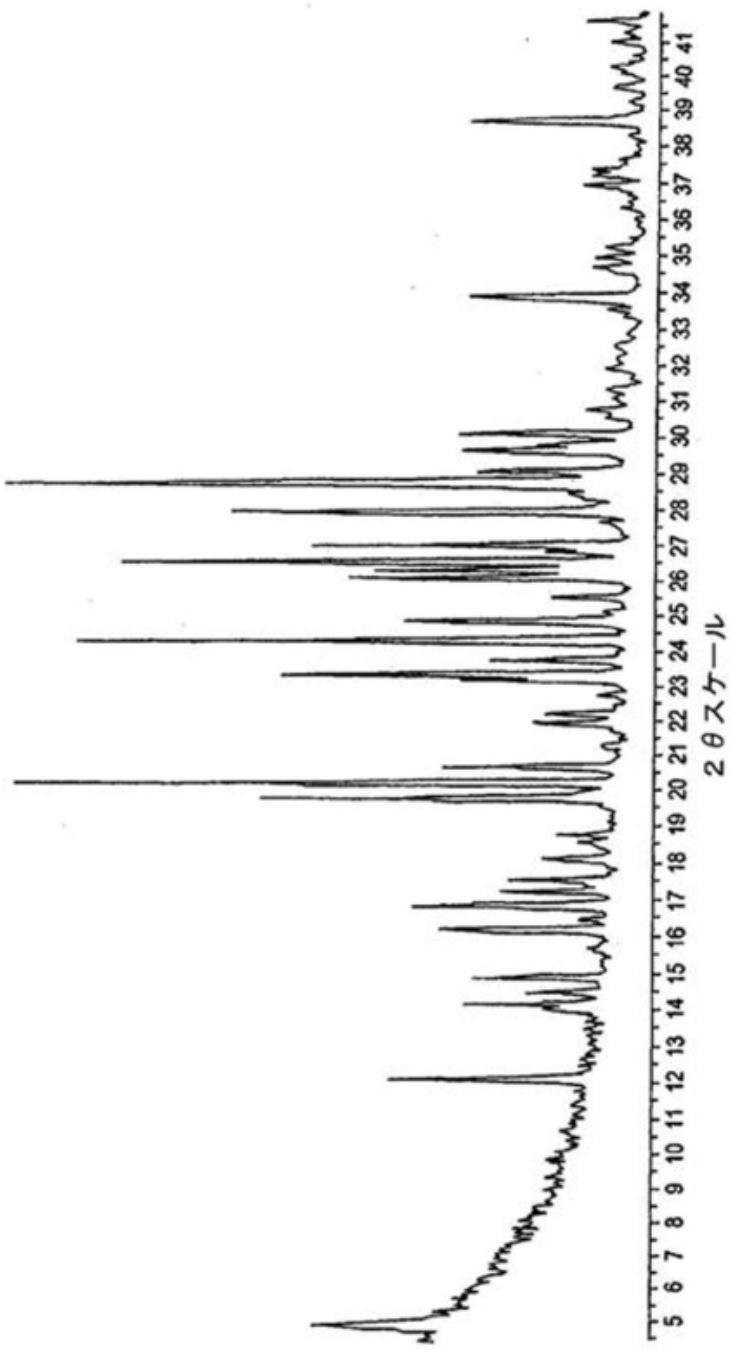
" to

"A Form 1 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction

pattern shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4.

FIG. 3

[Chemical 1]



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" (The underline added by the body indicates the amended part).

2. Suitability of amendment

Since the Amendment limits the X-ray diffraction pattern by amending "a X-ray diffraction pattern substantially shown in FIG. 3" that is a matter necessary to specify the invention recited in Claim 1 before the Amendment to "an X-ray diffraction pattern shown in FIG. 3" by deleting the word "substantially" and the field of industrial application of the invention and the problem to be solved by the invention remain unchanged, the Amendment falls under restriction of the scope of claims under Article 17-2(5)(ii) of the Patent Act.

Therefore, it is examined below whether the invention described in Claim 1 after the Amendment (hereinafter, referred to as the "Amended Invention") complies with the provisions of Article 126(7) of the Patent Act applied mutatis mutandis under Article 17-2(6) of the Patent Act (whether independently patentable at the time of filing the application).

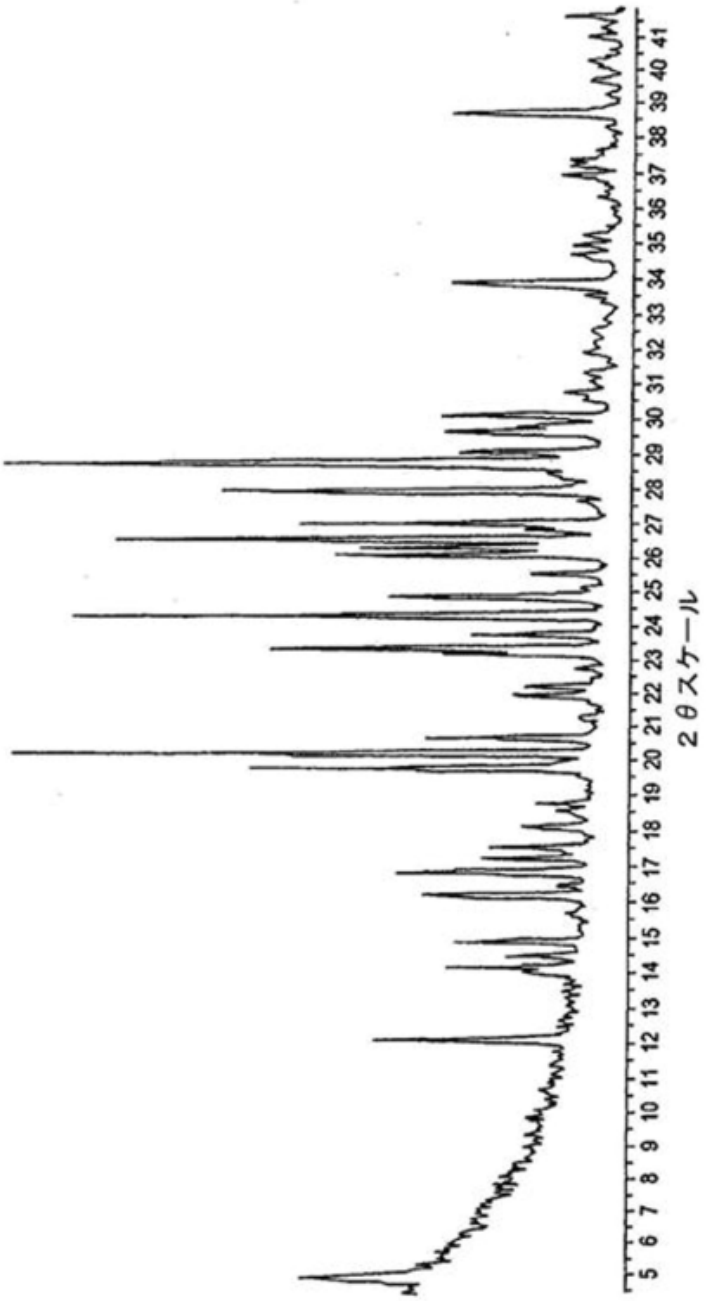
(1) Amended Invention

The Amended Invention is:

"A Form 1 polymorph of 5-amino-1-(4-(chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid, characterized by an X-ray diffraction pattern shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4.

FIG. 3

[Chemical 1]



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."

(2) Article 36(4)(i) of the Patent Act (Enablement requirement)

A Introduction

The examination below will be carried out from the following viewpoint.

Since "to work" the invention in the case of an invention of a product means an act of producing, using, assigning, etc. of the product (Article 2(3)(i) of the Patent Act), "as to enable ... to work the invention" (Enablement requirement) in Article 36(4)(i) of the Patent Act means that the product can be produced and used. Therefore, in order to comply with the enablement requirement, it is necessary that an invention of a product can be produced and used by a person skilled in the art based on the description or suggestion in the specification and common technical knowledge as of the time of filing the application.

B Descriptions in the detailed description of the invention and drawings

The detailed description of the invention and drawings of the present application (hereinafter, referred to as the "specification of the present application, etc.") has the following descriptions.

(A) Descriptions of the technical field, prior art, and the objectives of the invention

"[0002]

Field of invention

This invention is related to new chemical compounds of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof (referred herein as carboxyamidotriazoles or CAI), to formulations of 5-amino or substituted amino 1,2,3-triazole orotates as well as substituted derivatives thereof, (with defined base:acid ratios, CTOs), to formulation of 5-amino or substituted amino 1,2,3-triazoles orotate as well as substituted derivatives thereof and orotic acid, (with defined base:acid ratios, CAOs) and to safer processes or the preparation of the same, by using stable, more efficient, and safer starting materials to synthesize intermediate azide materials necessary in the synthetic pathways for CAI and the orotate formulations - CTO and CAO. More particularly, the invention relates to new polymorphs of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof. This invention still more particularly relates to novel 5-amino or substituted amino 1,2,3-triazoole orotates (CTOs with optimum base:acid ratios in the range 1:1 to 1.4) as well as formulations of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof and orotic acid (CAO) in optimum base:acid ratios of 1:1 to 1:4, and use of the same in the control and treatment of diseases including, but not limited to solid cancers, macular degeneration, retinopathy, chronic myeloid leukemia, AIDS, and diseases which rely on aberrant signal transduction and proliferation.

[Background Art]

[0003]

This invention is in the field of development of new polymorphs of 5-amino or substituted amino 1,2,3-triazoles (CAI) as well as substituted derivatives thereof, of orotates of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof, and of formulations of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof and orotic acid (in optimum ratios of base:acid). The objective is to develop new polymorphs of 5-amino or substituted amino 1,2,3-triazols as well as substituted derivatives thereof, to improve chemical, biological, pharmacokinetic, and toxicokinetic properties and improve therapeutic properties, including, but not limited to anticancer activity, antimetastatic activity, calcium-mediated signal transduction, antiangiogenic, anti-PI3, anti-COX2, apoptosis, down regulation of BCR-ABL protein in chronic myeloid leukemia, regulation of HIV LTR transcription, and anti-VEGF1 properties.

[0004]

In 1986, 5-amino or substituted amino 1,2,3-triazole compounds as well as substituted derivatives thereof were shown to have anticoccidial activity. US Pat. No. 4,590,201, issued to R. J. Bochis et el., 1986, describes a method of preparing 5-amino-1-(4-[4-chlooorobenzoyl]-3,5-dichlorobenzyl)-1,2,3-triazole-4 carboxamide (L6515182 or CAI) which includes use of sodium azide to synthesize one essential intermediate in the pathway, 3,5-dichloro-4-(4-chlorobenzoyl)benzyl azide. Subsequently, L651582 or CAI was shown to inhibit selected signal transduction pathways including those which involve calcium influx, the release of arachidonic acid, and the generation of inositol phosphates. US Pat. No. 5,359,078 issued to E. C. Kohn et al, 1994. "L651582" as used herein represents L6515182, CAI, Carboxyamidotriazole, NSC609974, or 99519-84-3 described in prior art.

[0005]

US Pat No. 5,912,346 issued to F. Wehrmann, 1999 then described inorganic and organic salts of L651582, and in particular described the process of preparing the orotate salt of L651582. The L651582 was prepared by the process described in US Pat. No. 4,590,201. The L651582: Orotate was in the ratio of 2: 1 (base:acid) as characterized by proton NMR and had a Melting Point of 234-235°C. As described above, the synthesis of the intermediate 3-(4-chlorobenzoyl)-4-chlorobenzyl azide was carried out using the intermediate 3-(4-chlorobenzoyl)-4-chlorovbenzyl bromide and sodium azide in ethanol. US Pat. No. 5,912,346 described improved antitumor activity of L651582 Orotate (CAI Orotate, base:acid 2:1) compared with that of equivalent dose

of L651582 in the androgen independent Dunning R-3227-AT-1 prostate cancer model in rats.

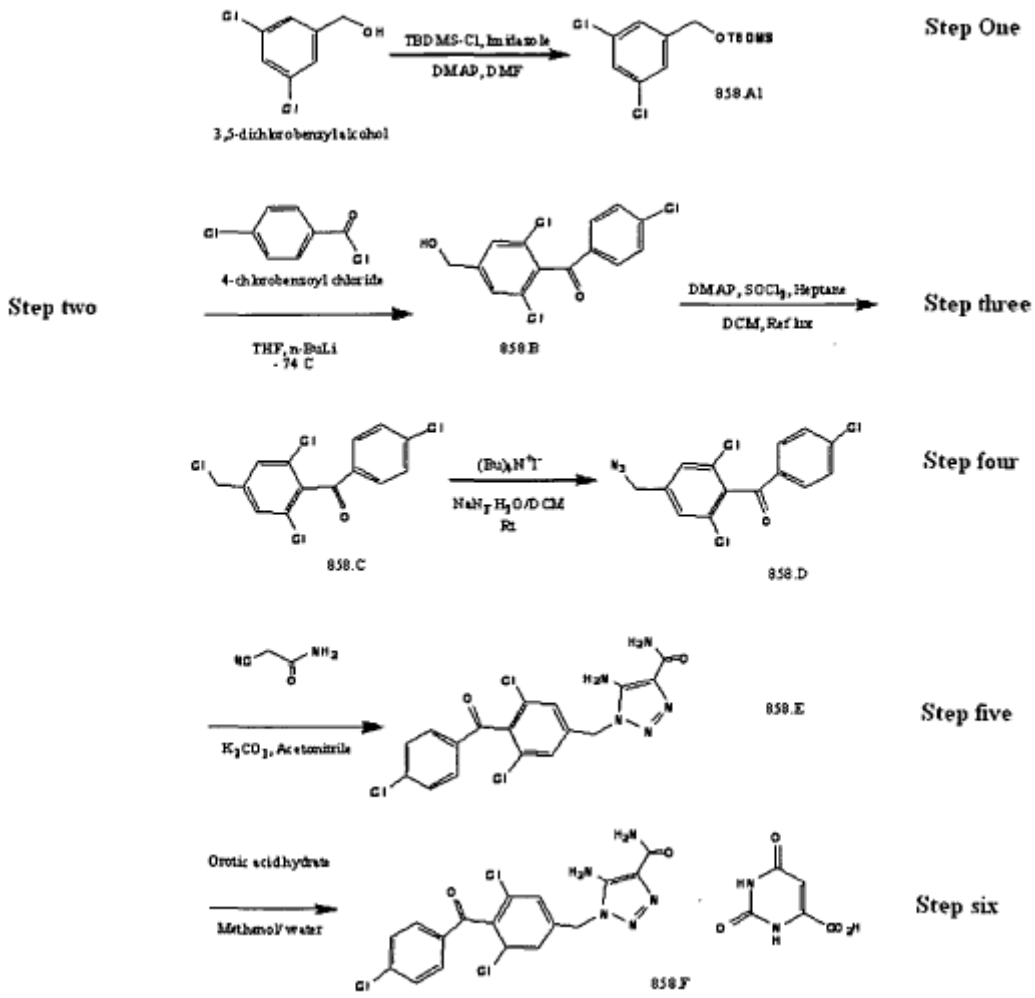
[0006]

Carboxyamidotriazole, L651582, CAI, NSC 609974, or 99519-84-3, an inhibitor of calcium-mediated signal transduction, is one of the first cytostatic signal inhibitory anticancer drugs discovered. It was tested in patients suffering from solid cancers in Phase I, Phase II, and Phase III trials at the National Cancer Institute. However, the NCI stopped the development of L651582 because it failed to demonstrate efficacy in human trials and/or was plagued by poor bioavailability, severe gastrointestinal toxicity, neurotoxicity, and problems of tolerability that prevented optimum dosing to achieve therapeutic effect. Capsules of micronized formulation of L 651582 in PEG400 were used in the clinical studies to improve bioavailability of the drug. Kohn EC et al., Clinical Cancer Res 7:1600-1609 (2001); Bauer KS et al., Clinical Cancer Res 5: 2324-2329 (1999); Berlin J et al., J Clin One 15: 781-789 (1997); Berlin J et al., Clinical Cancer res 8: 86-94 (2002); Yasui H et al., J Biol Chem 45:28762-28770 (1997); Alessandro R et al., J Cell Physiol 215: 111-121 (2008).

[0007]

Therefore, L651582 orotate (base:acid 2:1) described in US Pat. No. 5,912,346 represented a potential way to salvage this promising drug, L651582, by improving its efficacy, based on preclinical studies. However, problems were encountered in the scaling up of the process of preparing L651582 orotate (2:1 ratio) in bulk quantities, according to the method described in US Pat. No. 5,912,346.

[Chemical 1]



[0008]

With regard to the use of orotic acid in intensifying the analgesic effects of drugs, US Pat. No. 4,061,741 issued to Wawretschek W et al, 1977, describes use of dextropropoxyphene-HCl, laevopropoxyphen-HCI, or sodium salicylate in combination with choline orotate, and concludes that a drug formulation in combination with choline orotate gave the best effect. Clearly, prior art presents contradictory teachings about the proportions and chemical nature of orotic acid bonding with a chemical compounds.

[0009]

The synthesis scheme described in prior art for L651582 orotate is shown in Reaction Scheme I above. 858 is a product identifier, e.g., 858A to 858D represent intermediates. 858E represents carboxyamidotriazole (CAI). 858F represents carboxyamidotriazole: orotic acid or carboxyamidotriazole: orotate or CTO as defined herein.

[0010]

Prior art teachings suggested use of choline orotate in combination with the drug to be a preferred embodiment. Unfortunately, this did not address the problems encountered in the present invention of scaling up the production of CTO for clinical development. It was not clear if the base:acid ratio in L651582 orotate (2:1) was the optimum chemical structure for the drug. Moreover, problems were encountered when scaling up the production of L651582 orotate (2:1) to manufacture large quantities. Few manufacturers had the equipment and facilities required to handle bulk quantities of sodium azide, and those contractors that had the facilities charged large service fees.
[0011]

After protection of the alcohol group in 3,5-dichlorobenzyl alcohol, as the TBDMS ether step (step 1), the ether is reacted with 4 chlorobenzoyl chloride to form the substituted benzophene (step 2). The benzophene is treated with thionyl chloride (step 3) and then with sodium azide (step 4) to form 3,5-dichloro-4-(4-chlorobenzoyl)benzyl azide. Reaction of this azide with cyanoacetamide produces L651582 (step 5). Reaction of L651582 with orotic acid forms the L651582 orotate (2:1) (step 6).
[0012]

The use of sodium azide in the above process in step 4 was a serious drawback to scaling up the production of L6515182 orotate in large quantities. Handling of large quantities of sodium azide has to be done in special pressure sensitive reactors since sodium azide is a high energy content hazardous material. The special containment facilities required to handle sodium azide generally increased the cost of manufacture, because few drug manufacturers had the capacity to scale up the process to bulk amounts of the drug. This is because sodium azide is a rapidly acting, potentially deadly chemical that exists as an odorless white solid. When mixed with water or an acid, sodium azide changes rapidly to a toxic gas with a pungent odor. It also changes into toxic gas when it comes in contact with solid metals. Survivors of serious sodium azide poisoning may have heart and brain damage and the Center for Disease Control and Prevention advises victims to its Hotline immediately. (CDC - Facts About Sodium Azide, 2009). Clearly, there was need to develop a safer, new, affordable, and efficient process for the preparation of L651582 orotate without using sodium azide. Competitive bidding at affordable cost was impossible because sodium azide (Step 4) was required in the preparation of 3,5-dichloro-4-(4-chlorobenzoyl)benzyl azide, an intermediate, in the synthetic pathway for L651582 orotate, as shown above. It was therefore necessary to develop an alternate, safer, more efficient process to prepare the orotate drug with the optimum chemical configuration and base:acid ratio. The present

invention seeks to overcome these drawbacks.

[0013]

Even though L651582 orotate was demonstrated to have significantly higher antitumor activity in the prostatic cancer rat model (US Pat. No. 5912346), there was no teaching or suggestion regarding whether the chemical, pharmacological and biological properties of L651582 orotate in the base:acid ratio of 2:1 were optimum or not. Clearly, there is need to develop new polymorphs of CAI and an orotate compound of CAI that offers optimum chemical, biological, pharmacological, therapeutic, and toxicokinetic characteristics to justify clinical development.

[0014]

Thus, the primary objective of the invention was to develop an orotate formulation of CAI (wherein the base:acid ratio is in the range of 1:1 to 1:4) having improved effectiveness which is related to its bioavailability, which in turn is dependent on its solubility in human body fluids.

[0015]

Another objective of the invention was to develop a safer, more cost effective process to produce bulk quantities of CAI, CTO (as orotate of CAI) and CAO (as formulation of CAI mixed with orotate acid).

[0016]

An important objective of the invention was to make a safer CAI by using safer and less toxic ingredients to produce intermediates instead of using sodium azide or potassium azide which are highly toxic at very low concentrations. CAI produced by the processes described in prior art had been found to cause serious neurotoxicity and gastric toxicities in patients. Therefore, it was important to use of safer ingredients, and an improved process to produce has also resulted in production of new polymorphs of CAI and its orotate formulations."

(B) Description of the brief overview of the invention

"[Means for solving the problem]

[0018]

The present invention seeks to overcome drawbacks inherent in the prior art by providing compositions of new polymorphs of 5-amino or substituted amino 1,2,3-triazole as well as substituted derivatives thereof (referred herein as carboxyamidotriazoles or CAI); to formulations of 5-amino or substituted amino 1,2,3-triazoles orotates as well as substituted derivatives thereof, (with defined base: acid ratios, CTOs); and to formulations of 5-amino or substituted amino 1,2,3-triazoles

orotates as well as substituted derivatives thereof and orotic acid, (with defined base:acid ratios, CAOs).

[0019]

The present invention provides safer processes of the preparation of the same, by using stable, more efficient, and safer starting materials to synthesize intermediate azide materials necessary in the synthetic pathways for CAI and the orotate formulations - CTO and CAO.

[0020]

More particularly, the invention relates to new polymorphs of 5-amino or substituted amino 1,2,3-triazoles (CAI) as well as substituted derivatives thereof. CAI is present in several polymorph forms, including, but not limited to Form 1 and Form 2.

[0021]

This invention still more particularly relates to novel 5-amino or substituted amino 1,2,3-triazoles orotates (CTOs with optimum base:acid ratios in the range 1:1 to 1:4) as well as formulations of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof and orotic acid (CAO) in optimum base:acid ratios, orotates (CTOs) as well as substituted derivatives thereof.

[0022]

In another aspect, the invention relates to a process for preparing the intermediate azide materials necessary in the synthetic pathways by using stable, safer, and affordable starting materials, including but not limited to diphenjylphosphoryl azide or trimethyl silyl azide, TMSN3, instead of sodium azide or potassium azide.

[0023]

More particularly, this invention relates to novel polymorphs of 5-amino or substituted amino 1,2,3-triazole as well as substituted derivatives thereof, their orotate derivatives (CTO) (base:acid ratio in the range of 1:1 to 1:4), and use of the same in the treatment of diseases including, but not limited to solid cancers, macular degeneration, retinopathy, chronic myeloid leukemia, AIDS, and diseases which rely on aberrant signal transduction and proliferation pathways such as voltage-independent calcium channel blocker, P13, COX2, BCR-ABL, apoptosis, HIV LTR transcription, or VEGF1.

[0024]

In view of the foregoing state of the art, the present invention provides orotate derivatives of novel 5-amino or substituted amino 1,2,3-triazole or carboxyamidotriazole orotates (CTO) containing therein a chemical organic moiety that increases their bioavailability, delivery to the target, and antitumor efficacy and reduces toxicity. Specifically, one class of carboxyamidotriazole orotates (CTOs) having an

ionic bonding in the ratio of in the range of about 1:1 to 1:4 (triazole: orotic acid) constitutes the new compounds of the invention.

[0025]

In addition, formulations of 5-amino or substituted amino 1,2,3-triazole (CAI) as well as substituted derivatives thereof, and orotic acid, (with defined base: acid ratios, 1:1 to 1:4, CAO's).

[0026]

In another aspect, the invention provides a process for the preparation of the azide intermediate 3,5-dichloro-4-(4-chlorobenzoyl)benzyl azide, without using sodium azide, but instead using diphenylphosphoryl azide (DPPA) or TMN3 or safer azide equivalents. DPPA is significantly safer than sodium azide and has been used to convert alcohols directly to azides, and therefore, eliminates a step (step 3 in the Scheme outlined above) in the synthetic pathway for CTO.

[0027]

Another objective of the invention is to increase the bioavailability of CTO when given orally or by other routes, in human and other mammals, and improving the delivery of CTO to the target, for example, by improving absorption, delivery, and transport through tissues, the blood brain barrier, and the choroid retina complex.

[0028]

Yet another object of the invention is to reduce toxicity of CTO and related compounds when administered as orotate salts by increasing the clearance of the drug from the blood, tissues, and organs.

[0029]

The invention can further be used to reduce drug interactions and side effects when the CTO or CAI in combination with orotic acid (CAO) are administered as formulations.

[0030]

Another objective of the invention is to provide compositions of CTO for treating human neoplasms, and particularly, primary or metastatic tumors, diseases involving neovascularization such as macular degeneration, retinopathy, diabetic retinopathy, chronic myeloid leukemia, AIDS, and diseases which rely on aberrant signal transduction and proliferation pathways such as voltage-independent calcium channel blocker, P13, COX2, BCR-ABL, apoptosis, HIV LTR transcription or VEGF1, and reducing the toxic secondary effects of the drug by reducing the levels of the drug in noncancerous tissues that are susceptible targets of drug toxicity, by 10% to 100% when compared with administration of L651582 or CAI.

[0031]

A preferred embodiment of the invention comprises CTO in the ratio of 1:1, base:acid, a more preferred embodiment in the ratio 1:2, and a most preferred embodiment of the invention comprises compositions of CTO (in the ratio of about 0.7:1.3) prepared by the new process of the invention, for treatment of diseases including, but not limited to, solid cancers, macular degeneration, retinopathy, and chronic myeloid leukemia, and modulation of signal transduction pathways, such as PI3, COX2, BCR-ABL, STATS, CrkL, apoptosis, HIV LTR transcription, VEGF1, or others."

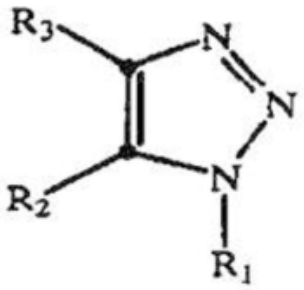
(C) Descriptions of 5-amino or substituted amino 1,2,3-triazole compounds, orotate compounds thereof, etc.

"[0033]

The present invention provides novel polymorphs of 5-amino or substituted amino 1,2,3-triazole or their substituted amino 1,2,3-triazoles (CAI) prepared by a novel process and include a class of compounds of formula I. The novel polymorphs of CAI include, but are not limited, to Form 1 and Form 2 as characterized by techniques such as NMR, DSC, FT-IR, and XRDP.

Formula I

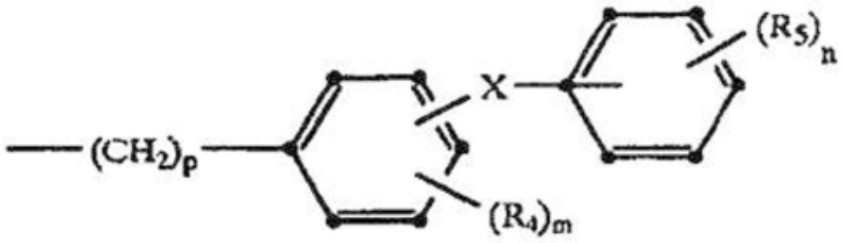
[Chemical 2]



[in which R_1 has the formula II, wherein,

R_1 is

[Chemical 3]



wherein p is 0 to 2, m is 0 to 4, and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR_6$ where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino or cyano; and, R_4 and R_5 are independently halogen (F, Cl, Br), cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono, or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido, or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino, or N-hydroxycarbamoyl; wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms.

[0034]

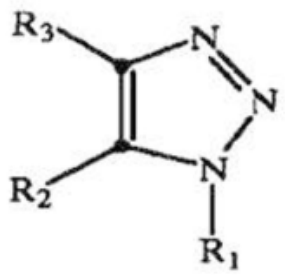
The 5-amino or substituted amino 1,2,3-triazole compound is reacted with orotic acid, to form orotate compounds of 5-amino or substituted amino 1,2,3-triazole compound in the ratio in the range of 1:1 to 1:4 (base:acid) by the improved and safer process of the invention to form CTOs for use according to the methods of the present invention.

[0035]

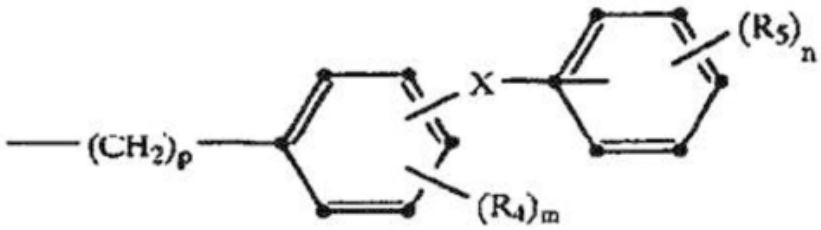
The novel polymorphs of CAI are further reacted with orotic acid to form orotate compounds of a class of compounds of formula II:

Formula II

[Chemical 4]



in which orotic acid is ionically bonded to R_2,
R_1 is
[Chemical 5]



wherein p is 0 to 2, m is 0 to 4, and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2, or $C=NR_6$, where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino, or cyano; and, R_4 and R_5 are independently halogen (F, Cl, Br), cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido, or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino, or N-hydroxycarbamoyl; wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms."

(D) Descriptions of the preferred embodiments of "CTO (orotate)"
"[0036]

The preferred embodiments of "CTO" as defined herein, have the empirical formula of $C_{22}H_{16}Cl_3N_7O_6$, molecular weight of 580.76), and two transition Melting Points, at 201°C and 236°C. CTO includes new polymorphs of CAI ionically bonded to orotic acid. CAI has many polymorphs, including, but not limited to Form 1 (Pattern 1)

and Form 2 (Pattern 2). The two embodiments of CTO have different transition melding points, for example, CTO (Form 1, Pattern 1) has Melting Points at about 136°C, 194°C, and 235 °C; and CTO (Form 2, Pattern 2) has Melting Points at about 137°C and 234°C. The two embodiments of CTO have a ^{1}H NMR spectrum consistent with the structure CAI: Orotic Acid (Fig. 1 and Fig. 2, respectively) and FT-IR patterns consistent with Form 1 and Form 2 (Fig. 3 and Fig. 4 respectively). CTO is crystalline as shown by X-ray powder diffraction patterns for Form 1 and Form 2 (Fig. 5 and Fig. 6 respectively).

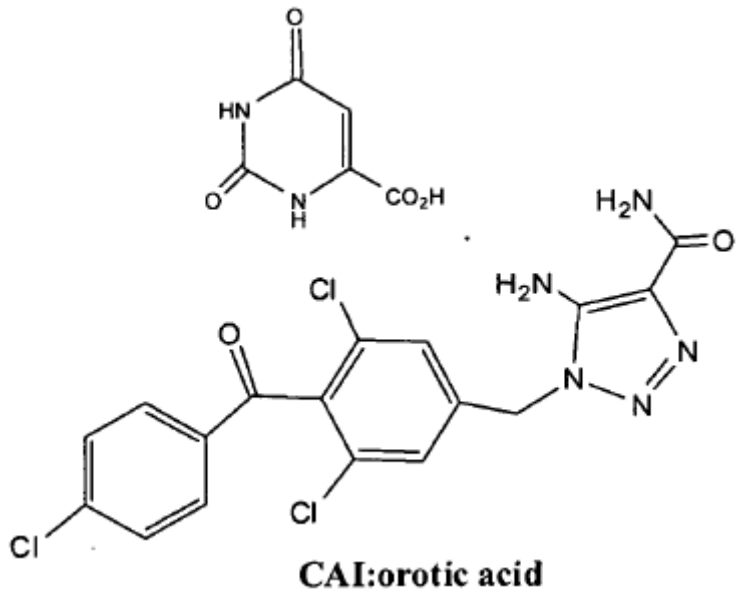
[0037]

Chemical names of the preferred embodiment of CTO include: 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, compound with orotic acid; 5-amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-12,3-triazole-4-carboxamide, compound with orotic acid; and 5-amino-1-{[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl}-1H, 1,2,3-triazole-4-carboxamide, compound with orotic acid.

[0038]

More particularly, the chemical structure of the polymorphs of CTO is:

[Chemical 6]



CAI:orotic acid

"

(E) Descriptions of the formulations

"[0039]

An additional embodiment includes the formulation of different polymorphs of

CAI and orotic acid (CAO). The new polymorphs of 5-amino or substituted amino 1,2,3-triazole (CAI) or 5-amino-1,2,3-triazoles or substituted amino 1,2,3-triazoles are mixed with orotic acid in the range of 1:1 to 1:4 (base:acid) to provide formulations of CAO used according to the methods of the present invention."

(F) Descriptions of methods for preparation

"[0040]

New Process:

The novel process of the invention wherein compounds of the invention can be prepared is shown in Reaction Scheme II below in five (5) steps. More specifically, the novel process uses diphenylphosphoryl azide to react with intermediate 858.B instead of with sodium azide. It eliminates step 3 in the prior art to form intermediate 858.C. See Scheme 1 above (six steps). The detailed processes are described in the Examples. 858.A through 858.F represent intermediate products and CTO as summarized below:

858.A represents t-Butyldimethylsilyl-3,5-dichlorobenzyl ether.

858.B represents 3,5-dichloro-4-(4-chrobenzoyl)benzyl alcohol.

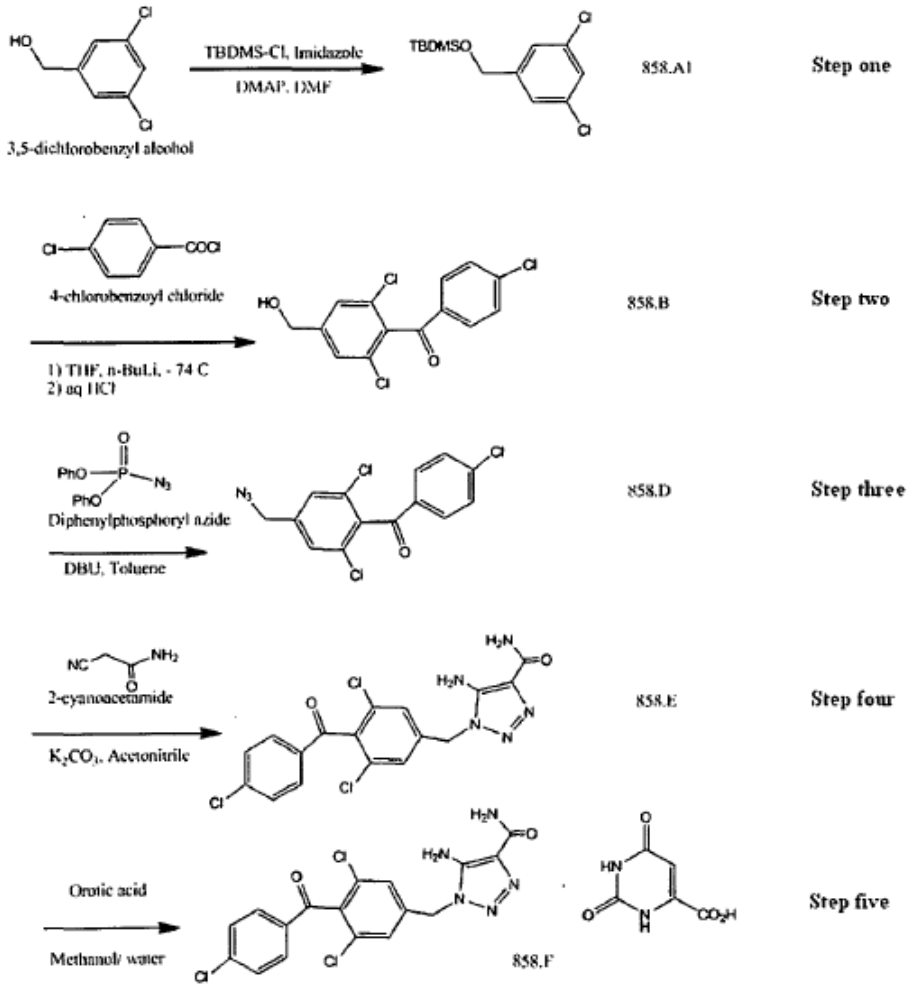
858.C represents 3,5-dichloro-4-(4'-chrobenzoyl)benzyl chloride.

858.D represents 3,5-dichloro-4-(4'-chrobenzoyl)benzyl azide.

858.E represents 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide.

858.F represents 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, compound with orotic acid, (CAI: Orotic acid) (CAI: Orotate) (CTO).

[Chemical 7]



[0041]

Importantly, it has been observed that different polymorphs of CAI, CTO, and CAO manufactured by the above process exhibit less gastric lesions and toxicity in rodents when compared with CAI which was synthesized by procedures described in the prior art. This may be related to the absence of use of toxic ingredients such as sodium azide and potassium azide.

[0042]

The new process has also resulted in the production of new polymorphs of CAI, CTO, and CAO. Thus, compounds of the invention include molecules that crystallize into more than one different crystal structure and exhibit different chemical properties of different polymorphs of CAI as characterized by techniques such as NMR, DSC, FT-IR, and XRDP (Figs. 1 to 6)."

(G) Descriptions of pharmaceutical compositions and formulations

"[0043]

Dosage and Formulation

5-amino or substituted amino 1,2,3-triazoles as well as substitute derivatives thereof have been manufactured into different polymorphs having chemical and biological properties that have overcome the disadvantages of CAI produced by procedures described in the prior art.

[0044]

In addition, 5-amino or substituted amino 1,2,3-triazole as well as substitute derivatives have been chemically reacted with orotic acid to form orotates (CTO) in the ratio 1:1 to 1:4 (base:acid), having unique bioavailability, pharmacokinetic properties, safety, and effectiveness.

[0045]

An alternate embodiment includes polymorphs of 5-amino or substituted amino 1,2,3-triazoles as well as substituted derivatives thereof, mixed with orotic acid, in the ratio 1:1 to 1:4 (base:acid) to form formulations of CAI and orotic acid (CAO).

[0046]

The above pharmaceutical compositions and formulations may be formulated into pharmaceutical preparations for administration to mammals for prevention and treatment of primary and metastatic neoplasms, chronic myeloid leukemia, macular degeneration, retinopathies, and other cell proliferative diseases. Many of the triazole orotate compounds may be provided as organic acid salts directly or with pharmaceutically compatible counterions, a form in which they are merely water-soluble. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. The therapeutic compounds or pharmaceutical compositions may be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, intrathecally, orally, rectally, topically, or by aerosol.

[0047]

Formulations suitable for oral administration include solid powder formulations; liquid solutions of the active compound dissolved in diluents such as saline, water, or PEG400; capsules or tablets, each containing a predetermined amount of the active agent as solid, powder, granules, or gelatin; suspensions in an appropriate medium; and emulsions.

[0048]

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile solutions, which contain buffers, antioxidants, and preservatives. The formulations may be in unit dose or multi-dose sealed containers.

[0049]

Patient dosages for oral administration of CTO range from 0.25-500 mg/day, commonly 25-100 mg/day, and typically from 50-400 mg/day. Stated in terms of patient body weight, usual dosage ranges from 0.005 to 10 mg/kg/day, commonly from 0.5-2.0 mg/kg/day, typically from 1.0 to 8.0 mg/kg/day. Stated in terms of patient body surface areas, usual dosage ranges from 0.1-300 mg/m^2/day, commonly from 20-250 mg/m^2/day, typically from 25-50 mg/m^2/day. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the anti-proliferative, antimetastatic effects, antiangiogenic effects, or other therapeutic effects in diseases which rely on aberrant signal transduction and proliferation.

[0050]

Doses may be adjusted depending on the route of administration, for example for intravenous, for inhalation/aerosol, for direct intraperitoneal or subcutaneous, for topical or, for intrathecal administrations.

[0051]

A variety of delivery systems for the pharmacological compounds may be employed, including, but not limited to, liposomes, nanoparticles, suspensions, and emulsions. The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0052]

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody, as nanoparticles and other forms. The liposomes or nanoparticles may be targeted to and taken up selectively by the tumor or other disease target.

[0053]

One of the most difficult properties to build into a newly discovered lead molecule is the desired pharmacokinetic profile, particularly in the case of orally dosed compounds.

'Most experienced medicinal chemists would prefer to start in a structural series that has inherently good pharmacokinetic properties, albeit with poor potency on the target receptor, and then set about improving the potency on the target, rather than working in the other direction,' 'Organic Chemistry in Drug Discovery, Drug Discovery (Organic Chemistry in Drug Discovery, Drug Discovery),' Science 303: 1810-1813 (2004).

[0054]

Improving the Bioavailability of CTO Administered orally.

The present invention relates generally to the method of increasing the oral bioavailability, delivery, and clearance of CTO, a unique orotate of L651582 in the ratio 1:1 to 1:4 (base:acid). The present invention provides processes to prepare orotate salts of water-insoluble drugs having an ionizable center, to improve the drugs' oral bioavailability, toxicology profile, and efficacy. Preferably the CTO is in the ratio 1:1 and more preferably it is in the ratio 1:2 and most preferably it is in the ratio 0.7:1.3.

[0055]

The absorption of drugs via the oral route is a subject to intense investigation in the pharmaceutical industry, since good bioavailability implies that the drug is able to reach the systemic circulation by mouth. Oral absorption is offered by both the drug properties and the physiology of the gastrointestinal tract, including drug dissolution from the dosage form, the manner in which the drug interacts with the aqueous environment and membrane, permeation across the membrane, and irreversible removal by first-pass organs such as the intestine, liver, and lung. Some pharmaceutical agents that exhibit low-solubility show poor bioavailability or irregular absorption, the degree of irregularity being affected by factors such as dose level, fed state, or the patient, and physicochemical properties of the drug.

[0056]

The majority of drug absorption occurs at the small intestine, because of the large surface area, since the presence of the villi and microvilli increases the absorptive area manifold. The circulation of the intestine is unique in that the intestine is the anterior or portal tissue that regulates the flow of substrates to the liver. The intestinal venous blood constitutes about 75% of the blood supply to the liver. Therefore, for drugs that are highly cleared by the intestine, the contribution of the liver, kidney, or lungs to drug metabolism will become reduced. Conversely, for drugs that are poorly extracted by the intestine, the substrate is able to reach the next organs, the liver, and the lung for removal. Therefore, the concentration of drug entering the intestine and the intestinal flow rate alter the rate of drug delivery and affect the rates of intestinal and clearance through hepatic first-pass metabolism.

[0057]

"Drug bioavailability" is defined here as the amount of drug systemically available over time. The present invention increases drug bioavailability of pharmaceutical agents by converting them into orotate salts. This may be achieved by altering the hydrophilic and lipophilic properties of the drug so that the drug permeates the membrane wall and blood perfusion rate becomes the overall rate-limiting step for

absorption, or by inhibiting drug biotransformation in the gut and/or by inhibiting active back transport systems in the gut that decrease the net transport of drugs across the gut membrane into the blood stream. In either case, the composition responsible for increased drug availability is the orotate salt of the pharmaceutical agent. For reasons that are not immediately apparent, it has been discovered that conversion of a water-insoluble L651582 into CTO (base:acid, 0.5:1 to 1:2) provides a method for increasing the bioavailability of an orally administered pharmaceutical agent to a mammal in need of treatment.

[0058]

Changes in the integrated systemic concentrations over time are indicated by area under the curve (AUC) or C_{max}, both parameters being well known in the art.

[0059]

The present invention provides methods wherein a composition provides an increase in bioavailability of the orotate salt of the pharmaceutical agent as measured by AUC of at least 25% to 100% relative to dosing of the pharmaceutical agent.

[0060]

The invention provides a composition that increases the bioavailability of the orotate salt of the pharmaceutical agent as measured by C_{max} of at least 50% to 100%.

[0061]

'Side effects' or 'toxicity' or 'adverse drug reactions' of chemotherapeutic agents are observed in the acute phase of chemotherapy administration and in patients cured of the cancer with subclinical tissue damage. There is a higher recognition of drug-related tissue side effects which may be quite severe, disabling, and irreversible. The clinician must be aware of the potential tissue/organ complications of chemotherapeutic agents, and where appropriate perform a baseline tissue examination before initiating the therapy.

[0062]

"Clearance" of drug occurs by perfusion of blood to the organs of extraction. "Extraction" refers to the proportion of drug presented to the organ which is removed irreversibly (excreted) or altered to a different chemical form (metabolism).

[0063]

The present invention provides a method to increase clearance of the orotate derivatives of CTO from noncancerous or normal tissues as measured by pharmacological studies at least 25% to 100% relative to dosing of the pharmaceutical agent.

[0064]

"Bioavailability" of a drug following oral dosing is the extent to which or the rate at which the active moiety of the drug or metabolite enters systemic circulation, thereby gaining access to the site of action. The physiochemical properties of a drug govern its absorptive potential, and binding to serum proteins. The efficacy of the drug depends on its interaction with the molecular target. Therefore, the properties of the dosage form partly depend on its chemical characteristics and on processes for manufacture of the drug in bulk quantities. Differences in bioavailability, efficacy, transport, and clearance among chemical formulations of a given drug can have clinical significance.

[0065]

"Absorption" rate is important even when a drug is absorbed completely; it may be absorbed too slowly to produce a therapeutic blood level quickly enough or so rapidly that toxicity results from high drug concentrations given to achieve the therapeutic level after each dose. Absorption occurs by one of three methods, passive diffusion, active transport, and facilitated active transport. Passive diffusion is simply the passage of molecules across the mucosal barrier until the concentration of molecules reaches osmotic balance on both sides of the membrane. In active transport the molecule is actively pumped across the mucosa. In facilitated transport, a carrier, generally a protein, is required to convey the molecule across the membrane for absorption. The present invention provides CTO compounds in chemical configurations that permit the drug to be delivered successfully to different tissues and organs and even cross the blood brain barrier, to reach the brain.

[0066]

Orotic acid, a free pyrimidine, is important in the synthesis of uridylate (UPP), a major pyrimidine nucleotide. Pyrimidines play a central role in cellular regulation and metabolism. They are substrates for DNA/RNA biosynthesis, regulators of the biosynthesis of some amino acids, and cofactors in the biosynthesis of phospholipids, glycolipids, sugars, and polysaccharides. The classical de novo pyrimidine biosynthetic pathway ends with the synthesis of UMP. Biochemistry, ed. Lubert Stryer, ed. W.H. Freeman & Co, NY, 4th ed, 739-762 (1995). The present invention provides a class of CTO that undergo dissolution to release the drug as a charged molecule and free orotic acid, which may prevent binding of the drug to proteins and facilitate transport to the target and rapid clearance.

[0067]

The invention provides embodiments showing increased effectiveness of the CTO as measured by improvement in 1) efficacy of CTO compared with formulation of equivalent dose of CAI + orotic acid, 2) bioavailability and clearance of CTO when

given as encapsulated solid CTO compared to CTO in PEG-400, 3) transport of orally administered CTO to the brain through the blood brain barrier, 4) transport of orally administered CTO to different eye issues, including the choroid-retina complex and vitreous humor in dogs.

[0068]

Importantly, the preclinical toxicity of CTO was determined in dogs by the PO route at 175, 350, 1025 mg/kg/day, and no deaths occurred after 28 days."

(H) Descriptions of working examples

"[Examples]

[0069]

Example 1

4-chlorobenzoyl chloride

3,5-dichlorobenzyl alcohol (1 mole) was treated with tert-butyldimethylsilyl chloride (1.05 mole), Imidazole, 99% (2.44 mole), and 4-dimethylaminopyridine in N, N-dimethylformamide at cold temperatures to produce t-butyldimethylsilyl-3,5-dichlorobenzyl ether (858. A1) at the extraction work-up.

[0070]

Example 2

3,5-dichloro-4-(4-chlorobenzoyl)benzyl alcohol

t-butyldimethylsilyl-3,5-dichlorobenzyl ether (858. A1) (1 mole) was reacted with n-butyllithium 1.6M solution in hexane followed by 4-chlorobenzoyl chloride, (1.01 mole), in tetrahydrofuran, while cold and the intermediate was treated with aqueous hydrochloric acid to give 3,5-dichloro-4-(4-chlorobenzoyl)benzyl alcohol (858. B).

[0071]

Example 3

3,5-dichloro-4-(4-chlorobenzoyl)benzyl azide

3,5-dichloro-4-(4-chlorobenzoyl)benzyl alcohol (858. B) (1 mole) was reacted with diphenylphosphoryl azide (diphenylphosponic azide) (DPPA) (1.2 mole, and 1, 8-diazabicyclo [5,4,0] undec-7-ene (Synonym: DBU) (1.2 mole)) in toluene at cold temperature, followed by aqueous work-up and alcohol titration, to give 3,5-dichloro-4-(4'-chlorobenzoyl)benzyl azide (858.D). DPPA is an organic compound that is used in the synthesis of other organic compounds. Aust. J. Chem 26: 1591-1593 (1973). The stability of DPPA to heating is shown by its distillation at 157°C and by the fact that vigorous evolution of nitrogen is not observed until a temperature of 175°C is reached.

[0072]

Example 4

5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)1,2,3-triazole-4-carboxamide (CAI)

3,5-dichloro-4-(4'-chlorobenzoyl)benzyl azide (858.D) (1 mole) was reacted with cyanoacetamido (1.69 mole) in hot acetonitrile, and potassium carbonate, (6.2 mole) to give 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide (858.E).

[0073]

Example 5

5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, compound with orotic acid. (CAI: Orotic acid)

5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide (858.E) (1 mole) was reacted with orotic acid (1.03 mole) and methanol/water mixture to give 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, solid compound with orotic acid, (CAI: Orotic acid; 1:1), (CTO) (858.F), MW 580.76 g, having transitional melting points of about 151°C, 238°C , and 332°C measured by differential scanning calorimetry. The XRPD pattern indicates that the CTO is composed of crystalline and amorphous (polymorphic) material.

[0074]

Example 6

Comparison of Anticancer Activity of CTO (858. F) with CAI + Orotic Acid (1:1)

The effect of CTO M.W. of 580.8 and CAI M.W. of 424.6 + orotic acid M.W. of 156.1, was studied in s.c.-implanted HT29 human colon tumor xenografts in male, athymic NCr-nu/nu mice. 6-week-old mice were implanted with HT29 fragments and 13 days later were sorted into 3 groups of ten. For the next 14 days (13-26 days), Group 1 control (C) received the vehicle; Group 2 = 343 mg/kg/dose; Group 3 = 240 mg/kg/day CAI + 103 mg/kg/day orotic acid. At 41 days, the mean tumor volume (mm^3) was measured as shown below:

Group 1 (Control) = 1436 mm^3

Group 2 (CTO 343 mg/g/day) = 864 mm^3 (p = 0.0050, Gr 2 vs Gr 1)

Group 3 (CAI 250 mg/kg/day + Orotic acid 103 mg/kg/day) = 1268 mm^3 (p = 0.2706, Gr 3 vs Gr 1). These results suggest that CTO is more effective in inhibiting tumor growth than an equivalent amount of CAI and orotic acid that are not chemically reacted. However, CAI + orotic acid formulation did show some tumor inhibition.

[0075]

Example 7

Comparison of CTO given orally as solid in capsule or as liquid in PEG-400

The bioavailability of CTO (base: acid, 0.7:1.3) was determined by administering a single dose 685 mg/kg by capsule (Group 1) or by oral gavage in PEG400 (Group 2). Two dogs (1F/1M) were used in each group. Blood samples were collected at 0, 1, 2, 4, 8, 12, 24, 48, 72, and 92 hours. CAI was measured by HPLC/MS.

[0076]

Group 1 receiving capsule: Plasma concentrations after 1 hr were 155 and 174 ng/ml for male and female dogs, respectively. C_{max} was 5800 ng/ml at 12 hrs for male and 7950 ng/ml at 24 hrs for female. Half life was 18 hr and 22.7 hr and AUC values were 326 and 277 μg/ml., for male and female, respectively.

[0077]

Group 2 receiving gavage in PEG400: Plasma concentrations after 1 hr were 511 and 570 ng/ml for male and female dogs. C_{max} was 6634 bg/ml at 24 hrs for male and 5350 ng/ml at 24 hrs for female. Bioavailability was 81.8% of that in Group 1 (100%).

[0078]

These results show that CTO given as solid in capsule had a better absorption pattern and bioavailability than CTO in PEG400. Based on these and additional results, CTO will be administered as solid in capsules to patients.

[0079]

Example 8

CTO given orally to mice crosses the blood brain barrier.

CTO was given orally (in PEG400) to six-week-old mice sorted in two groups of 6. Two doses were administered - Group 1 = 513 mg/kg; Group 2 = 342 mg/kg. Eight hours after treatment with CTO, the mice were euthanized for measurement of CTO concentration (as CAI) in brain tissue.

[0080]

Results obtained were: Group 1 - CAI levels were 15167 ± 2372 ng/g tissue; Group 2 levels of CAI were 10950 ± 1704 ng/g tissue, both in the therapeutic range (6000 ng/ml). Since the CTO was administered orally, these results indicate that CTO crosses the blood brain barrier and reaches the target organ, the brain.

[0081]

The present invention is not to be limited in scope by the embodiment disclosed in the example, which is intended as an illustration of one aspect of the invention, and any methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description.

Such modifications are intended to fall within the scope of the appended claims."

(I) Descriptions of other embodiments

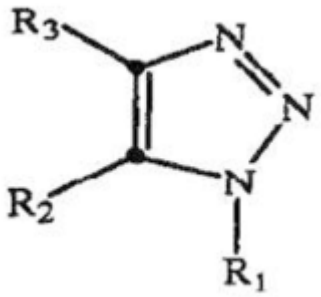
"[0082]

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

Other embodiments of the present invention may be as follows:

[1] A compound comprising polymorphic forms of a base having the formula:

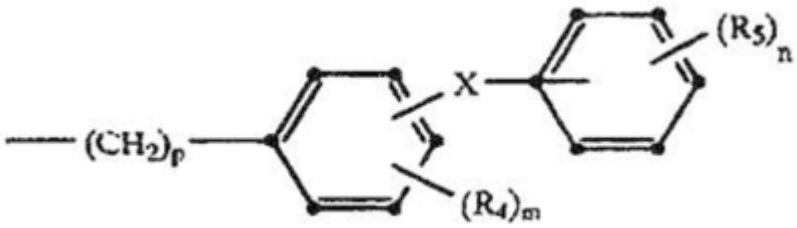
[Chemical 8]



[wherein,

R_1 is

[Chemical 9]



wherein p is 0 to 2; m is 0 to 4; and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2, or $C{=}NR_6$ where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino or cyano; and R_4 and R_5 are independently halogen (F, Br, Cl), cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio,

trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl, wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms.

[2] The compound of the above [1] which is 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide.

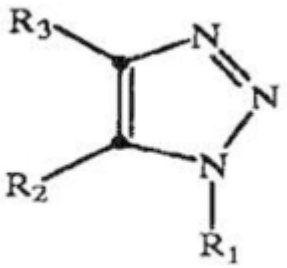
[3] The compound of the above [1] which is 5-amino-1-{[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl}-1H, 1,2,3-triazole-4-carboxamide.

[4] The compound of the above [1] which is 5-amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl-1H-1,2,3-triazole-4-carboxamide.

[5] The compound of the above [1], wherein the polymorphic forms include Form 1 and Form 2.

[6] An orotate compound comprising polymorphic forms of a base having the formula:

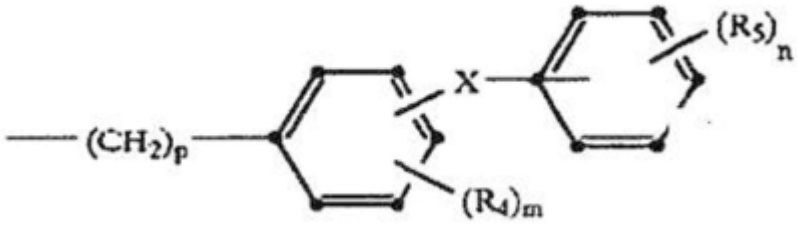
[Chemical 10]



[in which orotic acid is ionically bonded to R_2 in the range of 1:1 to 1:4, wherein,

R_1 is

[Chemical 11]



wherein p is 0 to 2, m is 0 to 4, and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2, or $C=NR_6$ where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino, or cyano; and R_4 and R_5 are independently halogen (F, Br, Cl), cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy,

carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino, or N-hydroxycarbamoyl, wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms.]

[7] The compound of the above [6] which is 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, bonded with orotic acid.

[8] The compound of the above [6] which is 5-amino-1-{[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide bonded with orotic acid.

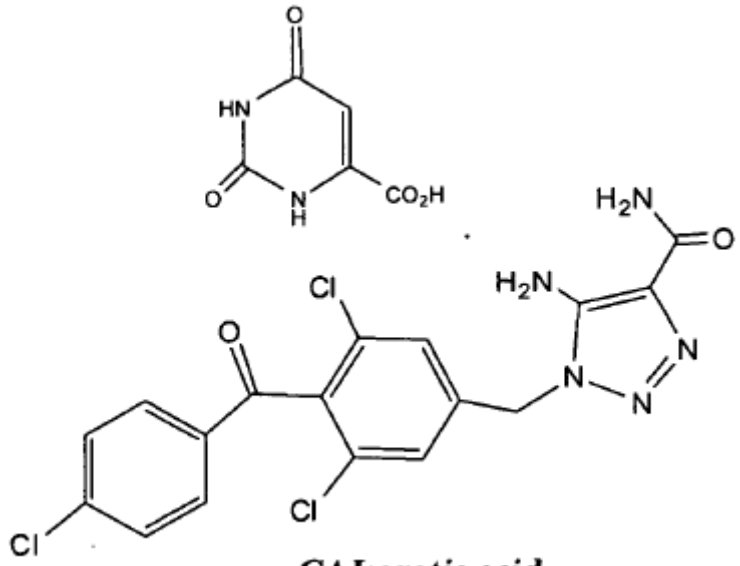
[9] The compound of the above [6] which is 5-amino-1-(3,5-dichloro-4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxamide, bonded with orotic acid.

[10] The compound of the above [6] in which the base: acid ratio is in the range of 1:1 to 1:4, preferably 1:1 and most preferably 0.7:1.3.

[11] The compound of the above [6], wherein the polymorphic forms include Form 1 and Form 2.

[12] A compound having the formula:

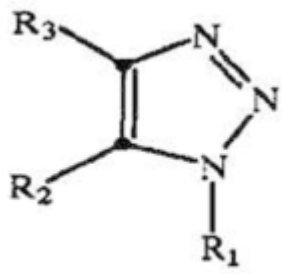
[Chemical 12]



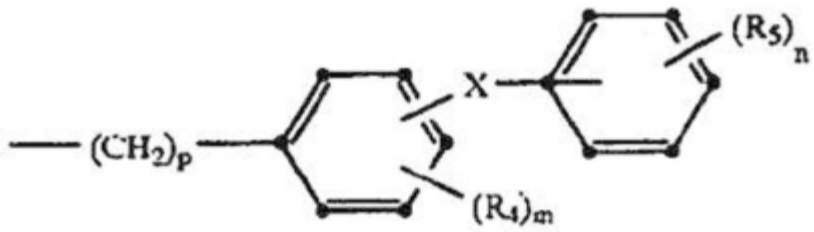
CAI:orotic acid

[13] A novel process for the preparation of a orotate compound comprising a base having the formula:

[Chemical 13]



[in which orotic acid is ionically bonded to R_2 in the range of 1:1 to 1:4, wherein,
R_1 is
[Chemical 14]



wherein p is 0 to 2, m is 0 to 4, and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2, or $C=NR_6$ where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino, or cyano; and R_4 and R_5 are independently halogen, cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino, or N-hydroxycarbamoyl, wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms], comprising the reaction of acetonitrile with 3,5-dichloro-4-(4'-chlorobenzoyl)benzyl azide in the presence of a base.

[14] The novel process in the above [13] in which the orotate compound is 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide bonded with orotic acid.

[15] The novel process in the above [13] in which the orotate compound is 5-amino-1-{[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl}-1H,1,2,3-triazole-4-carboxamide, bonded with orotic acid.

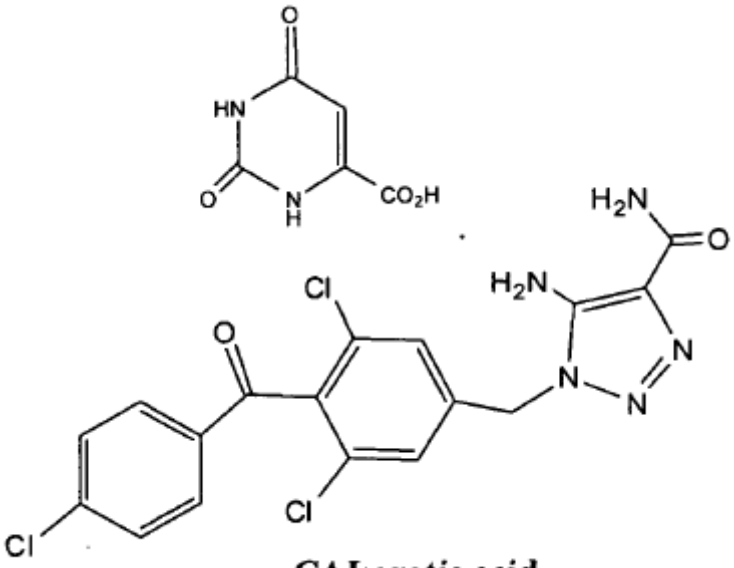
[16] The novel process in the above [13] in which the orotate compound is 5-amino-1-

(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxamide, bonded with orotic acid.

[17] The novel process in the above [13] in which the orotate compound has the base: acid ratio in the range of 0.5:1 to 1:2, preferably 1:1 and most preferably 0.7:1.3.

[18] The novel process in the above [13] in which the orotate compound has the base: acid ratio of 0.7:1.3 and the formula:

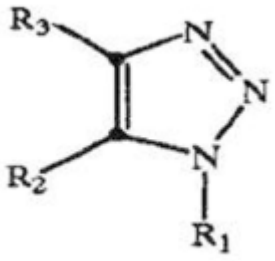
[Chemical 15]



CAI:orotic acid

[19] A novel process for the preparation of polymorphs of a base having the formula:

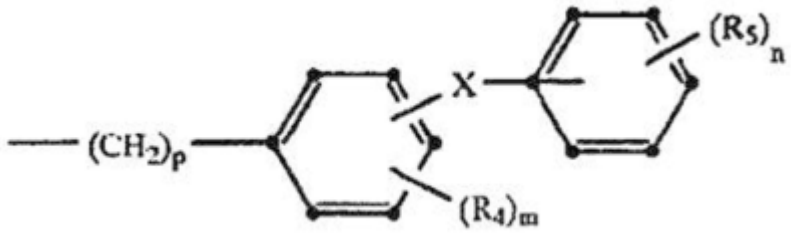
[Chemical 16]



[wherein,

R_1 is

[Chemical 17]



wherein p is 0 to 2, m is 0 to 4, and n is 0 to 5; X is O, S, SO, SO_2, CO, CHCN, CH_2, or $C=NR_6$ where R_6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, dilower alkylamino, or cyano; and R_4 and R_5 are independently halogen (F, Br, Cl), cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifluoromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R_2 is amino, mono or dilower alkylamino, acetamido, acetimido, ureido, formamido, formimido or guanidino; and R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl, wherein the lower alkyl, lower alkyl containing, lower alkoxy, and lower alkanoyl groups contain from 1 to 3 carbon atoms, comprising the reaction of acetonitrile with 3,5-dichloro-4-(4'-chlorobenzoyl)benzyl azide in the presence of base.

[20] The novel process in the above [19] in which the compound is 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide.

[21] The novel process in the above [19] in which the compound is 5-amino-1-{[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl}-1H,1,2,3-triazole-4-carboxamide.

[22] The novel process in the above [19] in which the compound is 5-amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxamide."

(J) Descriptions with respect to drawings

"[Brief description of drawings]

[0032]

[FIG. 1] illustrates the structure of CTO by NMR ad CAI:Orotic acid or CAI:Orotate, of a CTO sample J02642 having a Form 1 or Pattern 1 polymorph of CAI.

[FIG. 2] illustrates the structure of CTO by NMR ad CAI:Orotic acid or CAI:Orotate, of a CTO sample J02643 having a Form 2 or Pattern 2 polymorph of CAI.

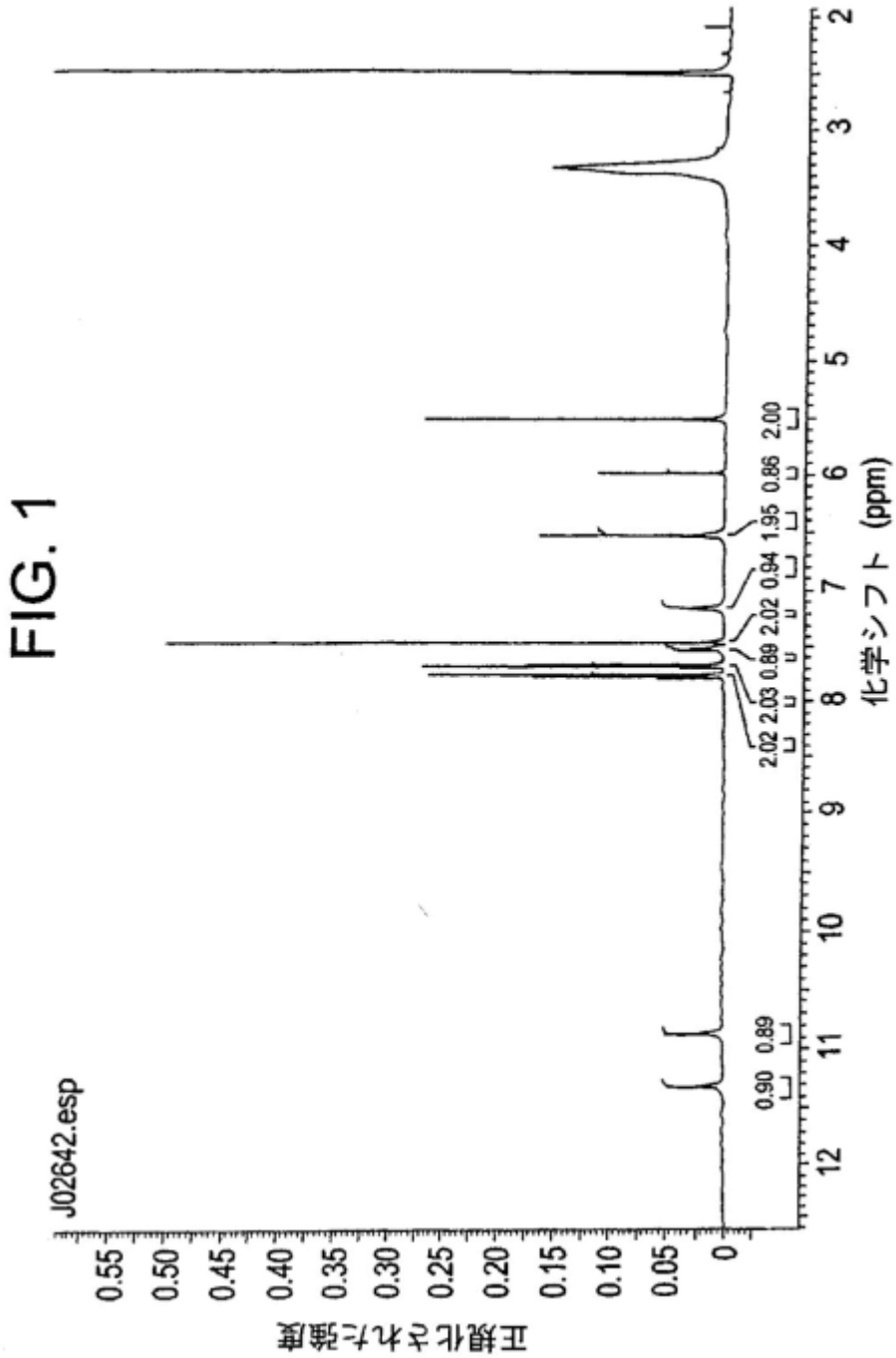
[FIG. 3] illustrates a high resolution diffractogram of CTO sample J02642 having Form 1 or Pattern 1 polymorph of CAI.

[FIG. 4] illustrates a high resolution diffractogram of CTO sample J02643 having Form

2 or Pattern 2 polymorph of CAI.
[FIG. 5] illustrates the FT-IR of CTO sample J02642 having Form 1 or Pattern 1 polymorph of CAI.
[FIG. 6] illustrates the FT-IR of CTO sample J02643 having Form 2 or Pattern 2 polymorph of CAI."

"[FIG. 1]

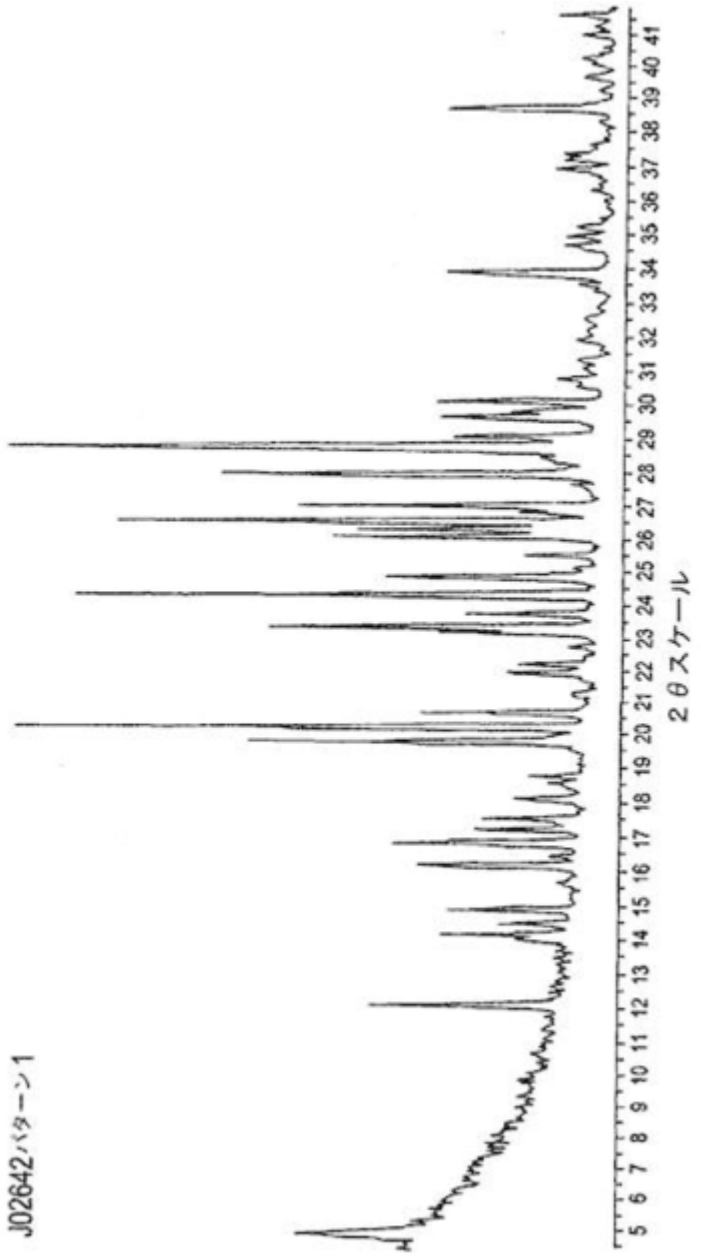
FIG. 1



化学シフト　　Chemical Shift
正規化された強度　　Normalized intensity
"

"[FIG. 3]

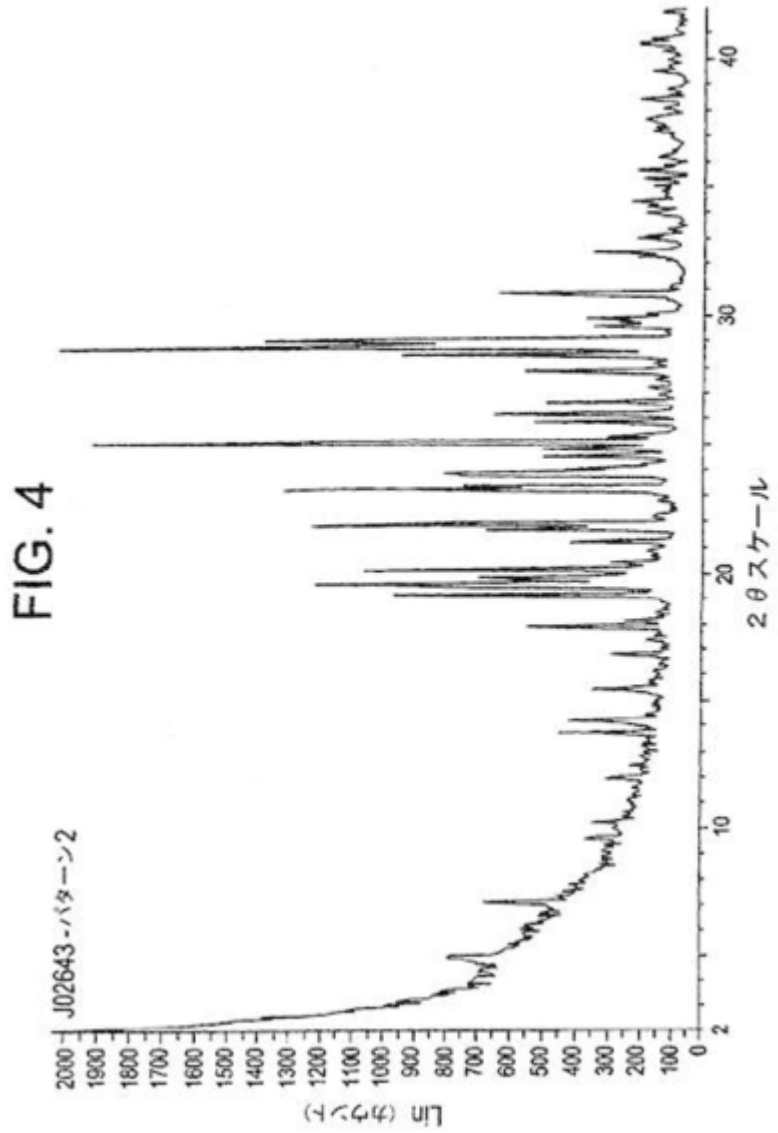
FIG. 3



２θスケール　　2θ Scale
パターン 1　　Pattern 1

"

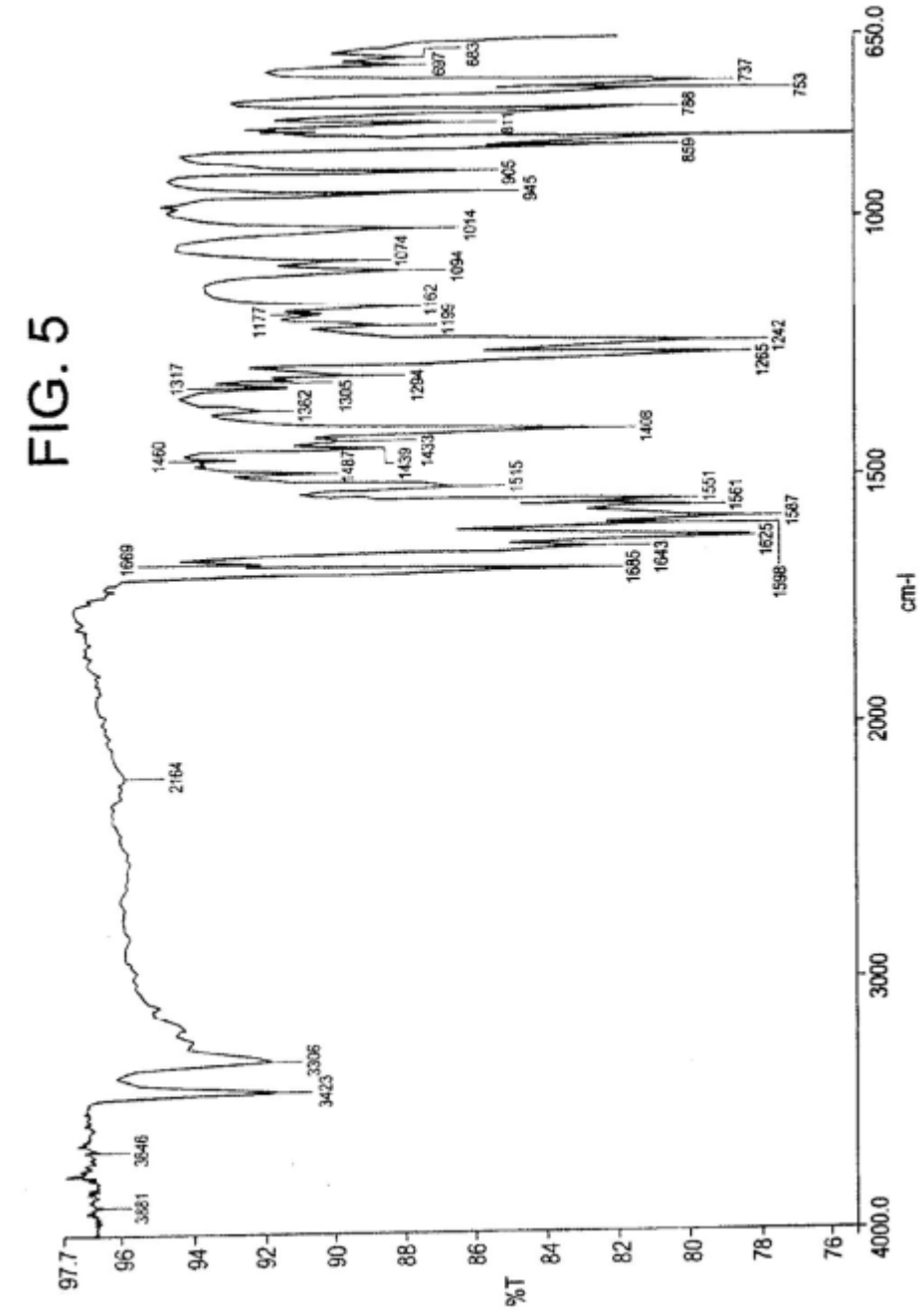
"[FIG. 4]



２θスケール　　2θ Scale
パターン 2　　Pattern 2
Ｌｉｎ（カウント）　　Lin (count)

"

"[FIG. 5]



"

C Examination

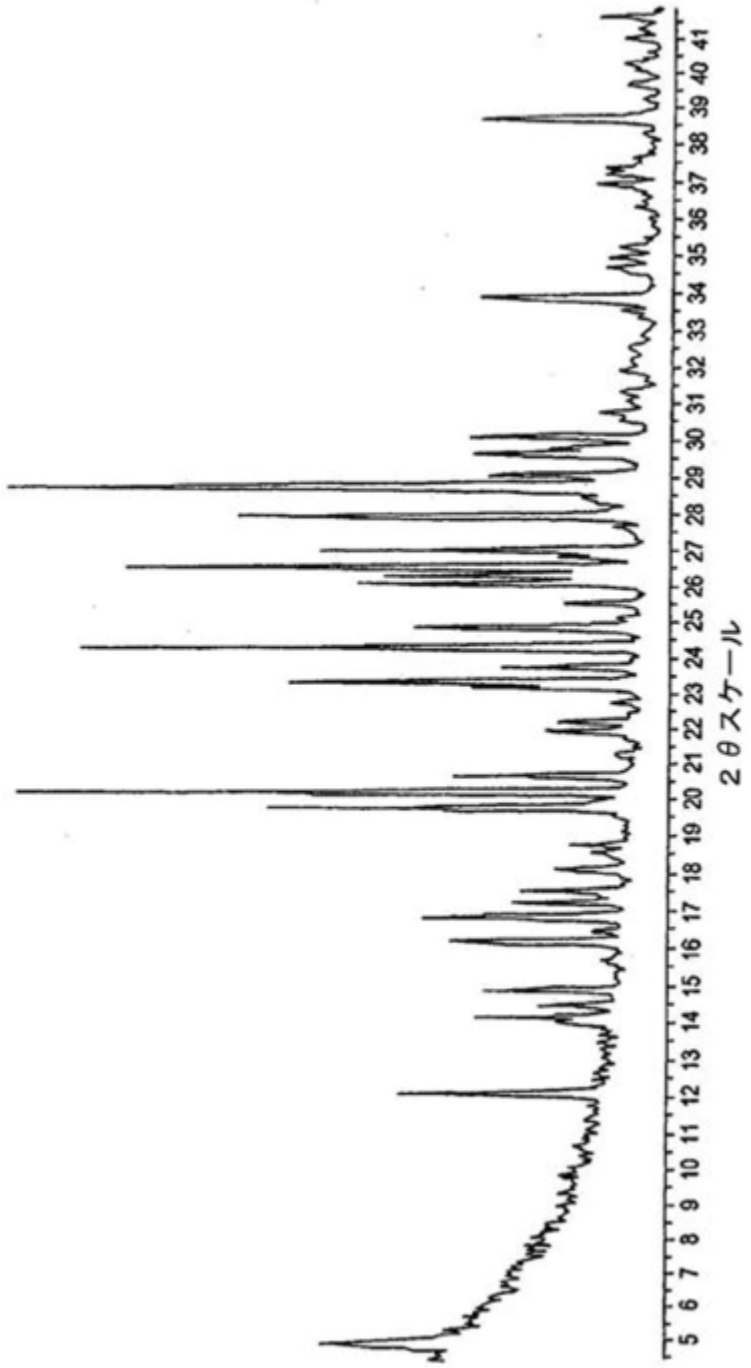
(A) As shown in above (1), the Amended Invention relates to:

"A Form 1 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction

pattern shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4

FIG. 3

[Chemical 1]



２θスケール　　2θ scale

."

Hereinafter, "5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide" is sometimes referred to as "Compound B."

(B) First, it is examined whether any concrete example that clearly indicates that "Form 1 polymorph of Compound B bonded to orotic acid characterized by an X-ray diffraction pattern shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4" (hereinafter, referred to as "polymorph of the Amended Invention") was produced is described in the detailed description of the invention.

As stated in above B, (A) to (J), the detailed description of the invention does not describe any concrete example as mentioned above.

Namely, descriptions that hint that polymorphs of the Amended Invention were produced are"[0036] The preferred embodiments of 'CTO' as defined herein, have the empirical formula of $C_{22}H_{16}Cl_3N_7O_6$, molecular weight of 580.76), and two transition Melting Points at 201°C and 236°C. CTO includes new polymorphs of CAI ionically bonded to orotic acid. CAI has many polymorphs, including, but not limited to Form 1 (Pattern 1) and Form 2 (Pattern 2). The two embodiments of CTO have different transition melding points, for example, CTO (Form 1, Pattern 1) has Melting Points at about 136°C, 194°C and 235°C; and CTO (Form 2, Pattern 2) has Melting Points at about 137°C and 234°C. The two embodiments of CTO have a ^1H NMR spectrum consistent with the structure CAI: Orotic Acid (Fig. 1 and Fig. 2, respectively) and FT-IR patterns consistent with Form 1 and Form 2 (Fig. 3 and Fig. 4 respectively). CTO is crystalline as shown by X-ray powder diffraction patterns for Form 1 and Form 2 (Fig. 5 and Fig. 6 respectively)" in the above B, (D), (Incidentally, it is recognized that the description includes erroneous descriptions in that FIG. 3 and FIG. 4 are mentioned as FT-IR patterns, and that FIG. 5 and FIG. 6 as X-ray diffraction patterns), "[FIG. 3] illustrates a high resolution diffractogram of CTO sample J02642 having Form 1 or Pattern 1 polymorph of CAI," "[FIG. 1] illustrates the structure of CTO by NMR ad CAI: Orotic acid or CAI: Orotate, of a CTO sample J02642 having a Form 1 or Pattern 1 polymorph of CAI" in the above B, (J), and "[FIG. 5] illustrates the FT-IR of CTO sample J02642 having Form 1 or Pattern 1 polymorph of CAI," but these descriptions do not describe any concrete method for producing the polymorphs of the Amended Invention.

(C) Next, it is examined whether a person skilled in the art can understand that working examples described in the detailed description of the invention can be understood such that polymorphs of the Amended Invention were produced notwithstanding that it is not

explicitly stated.

Working examples of production of compounds, or crystalline or amorphous materials are only Examples 1 to 5 in the above B, (H). Compound B is synthesized by Examples 1 to 4 (it is recognized that the title of Example 1 contains erroneous description), and subsequent Example 5 is described as follows:

"Example 5

5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, compound with orotic acid. (CAI: Orotic acid),

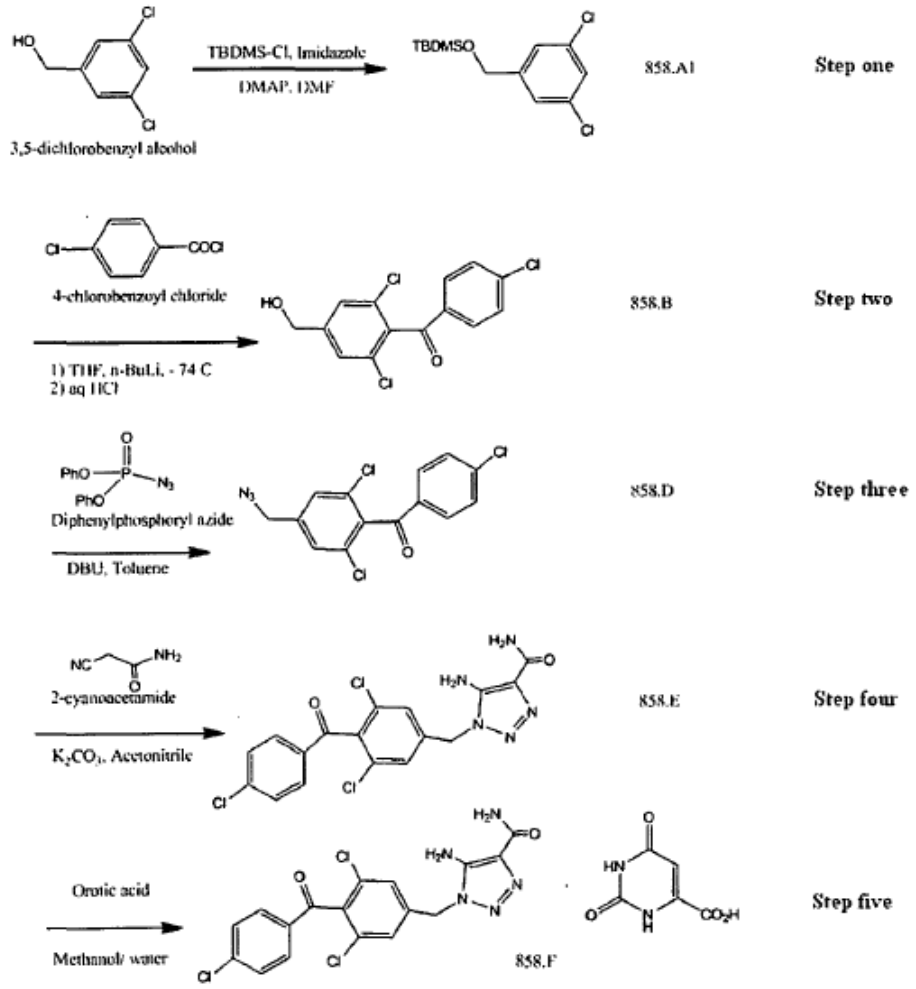
5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide (858. E) (1 mole) was reacted with orotic acid (1.03 mole) and methanol/water mixture to give 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, solid compound with orotic acid, (CAI: Orotic acid; 1:1), (CTO) (858. F)., MW 580.76 g, having transitional melting points of about 151°C, 238°C, and 332 °C, measured by differential scanning calorimetry. The XRPD pattern indicates that the CTO is composed of crystalline and amorphous (polymorphic) material."

The transitional melting points of about 151°C, 238°C, and 332°C described in Example 5, measured by differential scanning calorimetry do not coincide with any of two transitional melting points of 201°C and 236°C described in [0036], melting points of about 136°C, 194°C and 235°C of CTO (Form 1, Pattern 1), and melting points of about 137°C, and 234°C of CTO (Form 2, Pattern 2), and, therefore, a person skilled in the art cannot understand from the description "The XRPD pattern indicates that the CTO is composed of crystalline and amorphous (polymorphic) material " in Example 5 that the solid obtained in Example 5 is one of the polymorphs of the Amended Invention.

Accordingly, a person skilled in the art cannot understand that the working examples described in the detailed description of the invention show that polymorphs of the Amended Invention were produced notwithstanding that it is not explicitly stated.

(D) Next, it is examined whether any method to produce polymorphs of the Amended Invention is described in the detailed description of the invention so that a person skilled in the art could understand the same.

With respect to preparation method, there is a generic description of a scheme to produce a compound of Compound B with orotic acid (above B, (F)). Under a title of "New Process," the following scheme is described in paragraph [0040].



The Step 5 is a step in which "orotic acid" and "methanol/water" described above and below the arrow in the scheme respectively are added to Compound B to produce the compound of Compound B with orotic acid. Also, it is described in paragraph [0042] that "The new process has also resulted in the production of new polymorphs of CAI, CTO, and CAO. Thus, compounds of the invention include molecules that crystallize into more than one different crystal structure and exhibit different chemical properties of different polymorphs of CAI as characterized by techniques such as NMR, DSC, FT-IR, and XRDP (Figs. 1 to 6)."

Accordingly, this scheme can be deemed to be a generic description of the method for producing the polymorphs of the Amended Invention. However, nothing is described other than that orotic acid and methanol/water are added to Compound B to produce a compound of Compound B with orotic acid. In addition, it can be deemed that the description fails to discriminate not only polymorphs of the Amended Invention but also polymorphs that give the X-ray diffraction pattern of FIG. 4.

Then, it cannot be deemed that any method for producing polymorphs of the

Amended Invention is described in the detailed description of the invention so that a person skilled in the art can understand the same.

(E) It is examined in the light of common technical knowledge as of the date of filing the application whether a person skilled in the art could have produced the polymorphs of the Amended Invention.

Since it is necessary to set various conditions such as the ratio between Compound B and orotic acid, the ratio between methanol and water in the methanol/water, concentration, temperature, cooling speed, existence/non-existence of stirring, degree and time of stirring if stirred, and many other conditions in order to actually produce the polymorphs of the Amended Invention, it can be deemed in the light of common technical knowledge as of the date of filing the application that a person skilled in the art who reads the descriptions in the present specification shown in above B, (A) to (J) needed a large number of trials and errors beyond the reasonable extent that can be expected from a person skilled in the art.

(F) Appellant's allegations concerning above (B) to (E)

i With respect to above (C), the Appellant states that:

"Since Examples 1 to 5 are from small-scale production of experimental level (on the order of grams), a person skilled in the art must have understood that the methods used in Examples 1 to 5 are for experiments in laboratory for synthesizing a small amount of CTO and that test reagents and solvents used there are of laboratory grade that are allowed to comprise impurities. Accordingly, a person skilled in the art can understand that a minor differences in melting points are due to the level of impurities in CTO sample. On the other hand, XRPD patterns of Form 1 and Form 2 polymorphs of CTO described in claims of the present application were obtained from pure crystals produced from a pure ingredient (GMP grade for human use)" (Written opinion dated April 15, 2019 (hereinafter referred to as the "written opinion"), p. 4, l. 11 to 5 from the bottom), and that:

"Example 5 shows an embodiment carried out using laboratory grade test reagents and different conditions (non-GMP conditions). Reference 10 (Guidance for Industry, CGMP for Phase 1 Investigational Drugs, July 2008) attached to the present documents describes FDA's guidance concerning CGMP (Current Good Manufacturing Procedures) for industry. Reference 10 describes criteria for use of each substance described in certificates of analysis (p. 8, D), requirements for detailed producing procedures (p. 9, E), control of laboratories (p. 10, F), etc. It is clear from Reference 10

that Example 5 was carried out under non-GMP conditions and did not use substances approved in certificates of analysis.

With respect to melting points measured with differential scanning calorimetry (DSC), the Appellant believes that the reason why the melting point of CTO produced in Example 5 (non-GMP) differs from those of Form 1 and Form 2 polymorphs of CTO produced in accordance with Scheme II (GMP) is due to the difference in quality (degree of purity) of used ingredient or in conditions used for carrying out the process. Since the degree of purity of compounds affects melting points of the compounds and DSC is a reliable method for measuring purity as described in Reference 11 (Journal of Pharmaceutical and Biomedical Analysis, Vol. 49, Issue 3, pp. 627-631 (2009)) attached to this document (Written Amendment for amending the Written Demand for Appeal dated March 18, 2020 (hereinafter, referred to as the "Supplement for Reasons for Appeal"), p. 6, ll. 25 to 38), but the Appellant does not allege that the substance obtained by Example 5 is the polymorphs of the Amended Invention.

ii With respect to above (B), (D), and (E), the Appellant alleges as follows:
"2-1-1. ... the technological level of a person skilled in the art in the field of producing medicinal products for human use comprising CTO (CAI bonded to orotic acid) is as follows:
(1) In small-scale production of experimental level (on the order of grams) (for example, Examples 1 to 5 in the present specification), there are used ingredients and test reagent not in the grade for production and quality control standard (GMP) for medicinal products, but in laboratory grade allowing to comprise impurities.
(2) In large-scale production (on the order of kilograms), pure ingredients (GMP grade) must be used for producing medicinal products for human use.
(3) A person skilled in the art in the field of producing medical products for human use has technological knowledge on crystal polymorphs and can solve problems that may occur when a medicinal compound unexpectedly exhibits two or more polymorphs, etc. by slight modification of conditions of crystallization.

Accordingly, a person skilled in the art in the field of producing active ingredients (API) for medical products knows that significant changes in particle size distribution or crystal polymorph of API often occur if the production method is scaled up from laboratory scale to plant scale. These technological levels are described in Reference 1.
... Scheme II described in the present specification (paragraphs 0040 to 0042) shows a new process that includes 5 steps for producing Form 1 and Form 2 polymorphs of CTO

in mass-production scale.

The present specification does not describe any condition specific to production of each polymorph in Scheme II. However, it is explained below that, even if any unintended polymorph is formed by Scheme II, a person skilled in the art can produce intended polymorphs by applying a slight modification in operating Scheme II based on the above-described technological level.

First, the present specification describes sufficient information for identifying Form 1 and Form 2 polymorphs of CTO. To be concrete, paragraph 0036 of the present specification describes melting point of each polymorph, and paragraph 0032, FIG. 1 (J02642) and FIG. 2 (J02643) describe NMR patterns. FIG. 3 (J02642) and FIG. 4 (J02643) describe XRPD patterns, and FIG. 5 and FIG. 6 describe FT-IR.

...

Judging in consideration of descriptions in Reference 2, XRPD patterns of CTO shown in FIGS. 3 and 4 of the present application provide sufficient information for enabling a person skilled in the art to identify Form 1 and Form 2 polymorphs of CTO.

Based on the descriptions in the present specification, a person skilled in the art must have considered that each polymorph of CTO can be produced in accordance with Scheme II. Even if intended polymorphs cannot be obtained by Scheme II, a person skilled in the art can obtain intended polymorphs by applying the well-known 'inverse seeding' method described in Reference 3 (Organic Process Research & Development, 2000, 4, 413-417). Reference 3 describes two inverse seeding methods with respect to ritonavir (for Form 1, p. 417, right column, ll. 9 to 16; and for Form 2, p. 417, right column, ll. 21 to 27). Reference 3 describes an inverse seeding method (or reverse addition technique) that includes the following steps.

(Reference 3: p. 416, right column, l. 7 from the bottom to p. 417, left column, l. 13)

'A small amount of seeds was stirred in a required amount of reverse solvent. On the other hand, solution of the product was added slowly to a crystallizing solvent. Since a tiny amount of solution was added to a small amount of originally existing seeds, this delivered the same result as that of super-seeding. As the adding process progresses, products crystalized in sequence act as seeds, and the effect of an extreme example of super-seeding is given.'

...

Thus, based on the descriptions in the present specification (particularly, Scheme II) and the technological level (particularly, the inverse seeding method of Reference 3) of the technological field, a person skilled in the art can produce Form 1 and Form 2 polymorphs of CTO.

2-1-2. ...

However, paragraph 0040 of the present specification describes Scheme II that is a 'New Process.' Scheme II describes 5 steps for mass production, each of which respectively corresponds to 5 Examples in laboratory-scale (Examples 1 to 5 in the present specification, paragraphs 0069 to 0073). To be concrete, Steps 1, 2, 3, 4, and 5 of Scheme II respectively correspond to Examples 1, 2, 3, 4, and 5.

Since Examples 1 to 5 relate to small-scale production on the experimental level (on the order of grams), a person skilled in the art must have understood that the methods used in Examples 1 to 5 are for experiments in a laboratory for synthesizing a small amount of CTO, and test reagents and solvents used there are of laboratory grade that may comprise impurities. Accordingly, a person skilled in the art can understand that minor differences in melting points are due to the level of impurities in CTO sample. On the other hand, XRPD patterns of Form 1 and Form 2 polymorphs of CTO described in claims of the present application were obtained from pure crystals produced from a pure ingredient (GMP grade for human use)."

"2-1-3. ...

Based on paragraphs 0044 and 0073 (Examples) of the present specification and basic chemical principles, however, a person skilled in the art can understand a means for obtaining CTO with an intended ratio of CAI:orotic acid. For example, CTO with the ratio of 1:1 (CAI:orotic acid) can be produced using respectively about 1 mole of CAI and orotic acid. For CTO with the ratio of CAI to orotic acid 0.7:1.3, 0.7 mole of CAI and 1.3 mole of orotic acid are used, and this also applies to CTO with the CAI: orotic acid ratio of 1:1.86 covered by the CAI:orotic acid ratio (ratio of base to acid) of 1:1 to 1:4. CAI in CTO with CAI: orotic acid ratio of 1:4 consists of 1 mole CAI and 4 mole orotic acid. This procedure is simple, and the above ratio guarantees that the amount of orotic acid is larger than that of CAI.

It is important that, in FIGS 3 and 4 of the present specification, orotic acid has a peak at 2θ of 28.7. The reason is that orotic acid is ionically bonded to CAI and does not exist in the interplanar spacing of CAI. Even if the ratio of orotic acid becomes larger, the peak position of orotic acid 2θ remains at 28.7. This is the reason why polymorphs of CTO have the same diffraction pattern even if the CAI: orotic acid ratios are in the range of 1:1 to 1:4.

2-1-4. ...

Due to the above reasons, the inventions according to Claims 1 to 10 of the present application comply with the enablement requirement" (Written opinion, p. 2, l. 6 to p. 5, l. 34).

"4-1-3. ...

Due to all descriptions in the present specification and the reasons stated in the written opinion dated April 15, 2019, a person skilled in the art can reasonably understand how Form 1 and Form 2 polymorphs of CTO can be obtained.

The present specification describes Scheme II for producing CTO (paragraphs 0040 to 0042, and FIGS. 1 to 6). The present specification does not contain any concrete explanation of the difference in conditions specific to each polymorph in Scheme II. However, it has been explained in the written argument based on References 1 to 3 that even if any unintended polymorph is formed by Scheme II, a person skilled in the art can produce intended polymorphs by applying a slight modification in operating Scheme II using literature available as of the time of filing the application.

...

Reference 3 describes an 'inverse seeding' method for converting ritonavir from Form 2 to Form 1 in order to obtaining approval for production and sale. Based on common technical knowledge or well-known art concerning medicinal products that form polymorphs, a person skilled in the art can modify the inverse seeding method without carrying out a large amount of trials and errors or complicated experimentation beyond the reasonable extent that can be expected. As explained in the written opinion based on Reference 1. Reference 3 is used as a case study for teaching measures for solving the problem of converting a polymorph to a polymorph selected for human use to students in the fields of organic chemistry, chemistry for medicinal products and pharmacology. Accordingly, a person skilled in the art can reasonably understand that the inverse seeding method of Reference 3 (art so well known that there is no need for exemplify) can be applied to Scheme II for producing Form 1 and Form 2 polymorphs of CTO.

Based on the above, a person skilled in the art can produce polymorphs of CTO according to the present invention based on all descriptions in the present specification and common technical knowledge or well-known art.

4-1-4. ...

As stated above, based on all descriptions (especially, Scheme II) in the present specification and common technical knowledge (especially, inverse seeding method,) a person skilled in the art can produce Form 1 and Form 2 polymorphs of CTO according to the present invention. In addition, by adjusting the amount of CAI and orotic acid, CTO with desired ratio of base to acid (CAI:orotic acid ratio) can be produced.

4-1-5. ...

As stated in 4-1-4, it is self-evident that a person skilled in the art can understand from all descriptions in the present specification the means for obtaining CTO with the ratio of base to acid 1:1 to 1:4.

4-1-6. ...

... Since Reference 12 was available for a person skilled in the art as of the time of filing the present application, it belongs to common technical knowledge or well-known art available for a person skilled in the art to work the present invention based on all descriptions in the present specification. Reference 12 that explains polymorphism in detail describes that, in the medical product industry, more than half of active pharmaceutical ingredients crystalize as polymorphs or solvated compounds (p. 372, left column, third paragraph; right column, third paragraph; and, p. 373, left column, second and third paragraphs). In accordance with teaching by Reference 12 that has been cited by more than 140 pieces of literature, a person skilled in the art can reproducibly crystalize solid compounds.

In the written opinion dated April 15, 2019, Reference 3 that describes conversion of ritonavir from Form 2 to Form 1 was mentioned. Based on Reference 12 as common technical knowledge concerning medicinal products that form polymorphs, a person skilled in the art can modify the inverse seeding method. The written opinion pointed out steps (a) to (d) as a means for obtaining Form 1 and Form 2 polymorphs of CTO. These steps (a) to (d) are self-evident for a person skilled in the art by applying the inverse seeding method modified in accordance with Reference 12 to Scheme II of the present specification.

With respect to a question, "how the first seed crystal can be obtained," a person skilled in the art can obtain seed crystals in accordance with structure, function, and properties of each polymorph described in the present specification and drawings and Scheme II. Since polymorphism attracts a lot of interests and is well-known in the area of pharmaceuticals, a person skilled in the art can obtain seed crystals without carrying out a large number of trials and errors beyond the reasonable extent that can be expected based on well-known art of polymorphism ('polymorphism' is a fairly important keyword in life science industry, especially in the pharmaceutical industry) (Reference 12, p. 372, left column, second paragraph).

On the back of the following situation, the Appellant already had the novel crystal. At the time when the first lot of CTO was produced on a large scale using Scheme II under GMP conditions, there was no evidence that CTO existed as polymorphs. Therefore, a person skilled in the art did not have any motivation to carry out experiments for screening polymorphs. However, when the second lot of CTO was

produced at a different time, a different crystalline products were unexpectedly obtained. Therefore, experiments necessary for identifying characters of substances that exhibited polymorphism were carried out. Two types of polymorphs were identified for CTO. Based on the result of comparative study, Form 1 polymorph of CTO was chosen for clinical development. This Form 1 polymorph is the 'first seed crystal' that the Appellant already had.

4-1-7. ...

The present specification describes the present invention sufficiently so that a person skilled in the art can work the present invention. ... As stated above, based on all descriptions in the present specification (especially, Scheme II) and common technical knowledge (especially, the inverse seeding method), a person skilled in the art could have produce Form 1 and Form 2 polymorphs of CTO.

4-1-8. ...

As stated in 4-1-4, based on all descriptions in the present specification (especially, Scheme II) and common technical knowledge (especially, the inverse seeding method), and further by adjusting the amount of CAI and orotic acid, a person skilled in the art could have realized the situation in which orotic acid is superior to CAI.

4-1-9. ...

Due to reasons stated in 4-1-2 to 4-1-8, the Appellant believes that, since Reasons 1 and 2 of the examiner's decision have been resolved, that inventions according to Claims 1 to 10 comply with the enablement requirement and the support requirement" (Supplement for Reasons for Appeal, p. 5, l. 20 to p. 10, l. 31),

"The Appellant believed that, in examining the present application, the technological level of a person skilled in the art and common technical knowledge in the field of production of active pharmaceutical ingredient (API) for human treatment existing as polymorphs and crystalline products should be taken into consideration. While this technological level is common throughout the world, the Appellant made allegations based on the above technological level in prosecution history of a corresponding foreign patent application (Europe (Germany, France, U.K., Ireland, Italy, Switzerland, etc.)), and succeeded in getting a patent granted.

Technological level and common technical knowledge of a person skilled in the art in the technological field in Japan are on the level of common world standard, and a person skilled in the art can produce Form 1 and Form 2 polymorphs of the present invention without carrying out a large number of trials and errors beyond the reasonable extent that can be expected based on the above technological level, etc. and the description in the present specification.

... the present specification describes (1) production of 'Form 1 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction pattern shown in FIG. 3, wherein the ratio of base to acid is in the range between 1:1 and 1:4' (Claim 1), and (2) production of a 'Form 2 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction pattern shown in Figure 4, wherein the ratio of base to acid is in the range between 1:1 and 1:4' (Claim 4) . To be concrete, description (C) in the present specification (paragraphs [0033] to [0035]) describes name and structural formula of the compound in a form not contradicting the description in claims. Furthermore, the descriptions (D) in the present specification (D) (paragraphs [0036] to [0038]) describe transitional melting points of Form 1 and Form 2 polymorphs, and FIG. 3 and FIG. 4 of the present application describe XRDF of Form 1 and Form 2 polymorphs.

...

In this regard, description (F) in the present specification ([0040] to [0042]) describe procedures for producing Form 1 and Form 2 polymorphs stepwise.

...

In this regard, based on descriptions in the present specification, a person skilled in the art can produce Form 1 and Form 2 polymorphs in accordance with the New Process of Scheme II. Since a large number of medical compounds exhibit polymorphism, it can be deemed that technological level for handling medical compounds existing in two or more crystalline forms of chemists for medicinal products around the world is very high.

...

Reference 3 describes that (1) Form 1 ritonavir always crystalizes more quickly than Form 2 ritonavir, and (2) when the inverse seeding method using a desired crystal form was used in crystalizing step, formation of desired crystals depended on cooling conditions such as cooling temperature and cooling speed (conditions pointed out in the pre-examination report) (p. 417, left column, l. 2 from the bottom to right column, l. 27).

From the above descriptions (1) and (2) in Reference 3, a person skilled in the art can recognize crystallization condition for selectively produce Form 1 and Form 2 polymorphs of '5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide bonded to orotic acid' by subjecting the reaction mixture (prepared in accordance with Scheme II of the present specification) to a crystallization trial under differing cooling condition. Automated high throughput polymorph screening devices (that use Raman spectrometric method) for screening crystallization conditions by

carrying out crystallization trials under various cooling conditions were available to the general public as of the filing date of the present application (September 3, 2010) (Reference 13 attached to this written statement ...).

The present specification discloses sufficient information for identifying each Form 1 and Form 2 polymorph of '5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide bonded to orotic acid' (for example, FIG. 3 and FIG. 4). By using this information and the automated devices described in Reference 13, a person skilled in the art can carry out without carrying out a large number of trials and errors or complicated experimentation beyond the reasonable extent that can be expected decision on crystallization conditions for selectively produce each Form 1 and Form 2 polymorph '5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide bonded to orotic acid' and production of intended crystal form (including seed crystal for the inverse seeding method).

In other words, a person skilled in the art can produce each Form 1 and Form 2 polymorph of '5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide bonded to orotic acid' by 'modifying' cooling conditions described in Reference 3. Based on the technological level (Reference 13) as of the time of filing the present application when automated equipment that allows crystallization trials under various cooling conditions was available, a person skilled in the art could have realized the above 'modification' (To be concrete, to cool down to the temperature described in Reference 3).

Due to above reasons, the present invention complies with the enablement requirement" (Written statement dated October 28, 2020, p. 6,1-3, l. 2 to p. 8, l. 27).

It is recognized that the Appellant's allegation is such that, based on all descriptions in the present specification (especially, Scheme II) and common technical knowledge (especially, inverse the seeding method) as of the time of filing the application, a person skilled in the art could have produced polymorphs of the Amended Invention; that, by subjecting the reaction mixture prepared in accordance with Scheme II of the present specification, etc. to crystallization trials under differing cooling conditions, crystallization condition for selectively producing polymorphs of the Amended Invention could have been be recognized; and that, by using information sufficiently described in the present specification for identifying polymorphs of the Amended Invention and the automated high throughput polymorph screening devices, production of polymorphs of the Amended Invention could have been carried out without carrying out a large number of trials and errors or complicated experimentation

beyond the reasonable extent that can be expected.

It is as already stated in above (D), however, that the description of scheme II pointed out by the Appellant only describes that orotic acid and methanol/water are added to Compound B to generate a compound of Compound B with orotic acid as a reaction formula, and it cannot be deemed that scheme II describes the production method of polymorphs of the Amended Invention so that a person skilled in the art can understand the method. Even if Scheme II is read, it is not clear under what conditions the polymorphs of the Amended Invention can be concretely produced. In addition, it is recognized that the description in Scheme II relates to a production method common for two different polymorphs, Form 1 and Form 2 polymorphs, described in the present specification, etc., but it is not clear from the description in Scheme II how the polymorph of the Amended Invention (Form 1 polymorph) as one different from Form 2 polymorph characterized by X-ray powder diffraction pattern (FIG. 4) different from Form 1 polymorph is produced.

In addition, the method described in Reference 3 that describes the inverse seeding method according to Appellant's allegation explains polymorphs of a compound called ritonavir, and page 417, right column, lines 9 to 27 mentioned by the Appellant describes a crystallization method that starts from a solution of the compound in ethyl acetate and uses heptane, and then uses a seed (crystal seed), and the compound to be crystalized, solvent, and crystallization method are completely different from those in step 5 of the scheme in paragraph [0040] of the present specification (a step in which "orotic acid" and "methanol/water" described respectively above and below the arrow in the scheme are added to Compound B to produce the compound of Compound B with orotic acid).

Furthermore, even if the method described in Reference 3 is a well-known method, it is recognized that the seed (seed crystal) is necessary for carrying out the method, but the method for producing the seed crystal is not clear. The Appellant alleges that "a person skilled in the art can obtain the seed crystal in accordance with structure, function, and properties of each polymorph described in the present specification and drawings and Scheme II. Since polymorphism attracts a lot of interests and is well-known in the field of pharmaceuticals, a person skilled in the art can obtain the seed crystal without carrying out a large number of trials and errors beyond the reasonable extent that can be expected based on well-known art of polymorphism" (Supplement for Reasons for Appeal, p. 9, ll. 5 to 8), but it cannot be deemed from what was stated above that, even if the description in Scheme II is read,

the seed crystal for producing polymorphs of the Amended Invention can be produced.

In general, even if there could be a case in which desired polymorphs can be selectively produced by selecting cooling condition in crystallization, it cannot be known from description in the present specification, etc. what cooling conditions should be selected, and, as stated above (E), since it is necessary to set various conditions such as the ratio between Compound B and orotic acid, the ratio between methanol and water in the methanol/water, concentration, temperature, cooling speed, existence/non-existence of stirring, degree and time of stirring if stirred, and many other conditions in order to actually produce the polymorphs of the Amended Invention, it cannot be deemed that, even if an automated high throughput polymorph screening device is used, production of polymorphs of the Amended Invention can be carried out without carrying out a large number of trials and errors or complicated experimentation beyond the reasonable extent that can be expected.

Furthermore, the Appellant also alleges that "On the back of the following situation, the Appellant already had the novel crystal. At the time when the first lot of CTO was produced on a large scale using Scheme II under GMP conditions, there was no evidence that CTO existed as polymorphs. Therefore, a person skilled in the art did not have any motivation to carry out experiments for screening polymorphs. However, when the second lot of CTO was produced at a different time, different crystalline products were unexpectedly obtained. Therefore, experiments necessary for identifying characters of substances that exhibited polymorphism were carried out. Two types of polymorphs were identified for CTO. Based on the result of comparative study, Form 1 polymorph of CTO was chosen for clinical development. This Form 1 polymorph is the 'first seed crystal' that the Appellant already had" (Supplement for Reasons for Appeal, p. 9, ll. 11 to 18). But, whether the appellant already had the novel crystal cannot be any direct ground for satisfaction of the enablement requirement by the Amended Invention, and, production conditions for the second lot of the above allegation are not known, and it is not clear under what production conditions the polymorphs of the Amended Invention were obtained.

In addition, whether CTO with the ratio of base to acid of 1.1 to 1.4, which the Appellant deems to be a premise for satisfaction of the enablement requirement, can be produced (assuming that such CTO can be manufactured) and whether any crystal that has a given X-ray diffraction pattern can be produced are different matters, and no technological ground has been shown for the allegation, and as well no technological ground has been shown for the allegation, "It is important that, in FIGS 3 and 4 of the present specification, orotic acid has a peak at 2θ of 28.7. The reason is that orotic acid

is ionically bonded to CAI and does not exists in the interplanar spacing of CAI. Even if the ratio of orotic acid becomes larger, the peak position of orotic acid 2θ remains at 28.7. This is the reason why polymorphs of CTO have the same diffraction pattern even if the CAI: orotic acid ratios are in the range of 1:1 to 1:4" (Written argument, p. 5, ll. 9 to 13). Right from the beginning, although it can be deemed that, if polymorphs of Compound B bonded to orotic acid have the same X-ray diffraction pattern in all ratios of base to acid (however, within the range of 1:1 to 1:4), it means that the ratio of base to acid does not cause the interplanar spacing of crystal structure to change. But, technological relation between the fact that Compound B and orotic acid are ionically bonded and the fact that the interplanar spacing is not caused to change is not clear, and there was no common technical knowledge as of the time of filing the application that the interplanar spacing does not change for all ratios of base to acid, and, since it can be deemed that, even if the peak exists at 2θ of 28.7° in both of FIG. 3 and FIG. 4, they are different diffraction patterns from each other as a whole drawing, the fact that the peak exists at 2θ of 28.7° in both of FIG. 3 and FIG. 4 cannot be any ground for an allegation that polymorphs of Compound B bonded to orotic acid have same X-ray diffraction pattern in the range of the ratio of base to acid from 1:1 to 1:4.

(G) According to the above, it cannot be deemed that a person skilled in the art could have produced the polymorphs of the Amended Invention based on descriptions or suggestions in the detailed description of the invention and common technical knowledge as of the time of filing the application. Therefore, with respect to the Amended Invention, it cannot be deemed that the detailed description of the invention is described sufficiently clear and complete so that a person skilled in the art can work the invention.

D Summary

As explained above, since it cannot be deemed that the detailed description of the invention describes the Amended Invention sufficiently clear and completely so that a person skilled in the art can work it, the description in the detailed description of the invention does not comply with the provisions of Article 36(4)(i) of the Patent Act.

(3) Article 36(6)(i) of the Patent Act (Support requirement)

A Introduction

The examination below will be carried out from the following viewpoint.

Whether the recitation in the scope of claims complies with the requirement

provided for in Article 36(6)(i) of the Patent Act (so-called "support requirement for specification") should be determined by comparing the recitation in the scope of claims and the description in the detailed description of the invention to examine whether the invention recited in the scope of claims is identical with the invention described in the detailed description of the invention, whether the invention is within the scope in which a person skilled in the art can recognize that the problem to be solved by the invention can be solved with descriptions or suggestions in the detailed description of the invention, and whether the invention is within the scope in which a person skilled in the art can recognize that the problem to be solved by the invention can be solved in the light of common technical knowledge as of the time of filing the application even without the descriptions or the suggestion.

B Descriptions in the detailed description of the invention and drawings

As described in above (2), B.

C Problem to be solved by the Amended Invention

According to above (2), B, (A) and (B), it was known from literature that L6515182 orotate of conventional art (with the ratio of base to acid, 2:1) (Note by the appeal decision: "L6515182" is Compound B) has anti-tumor activity, but there was no teaching or suggestion whether chemical, pharmacological, and biological properties of L6515182 orotate with the ratio of base to acid of 2:1 was optimal; therefore, it was necessary to develop novel polymorphs of CAI (Note by the appeal decision: Compound B) and orotate compounds of CAI that provide optimal chemical, biological, pharmacological, therapeutic, and toxicokinetic features. In addition, production of L651582 of prior art had a problem of use of highly toxic sodium azide for producing intermediates. Thus, primary objective of the invention of the present application is to develop orotic acid formulations (the ratio of base to acid is within the range of 1:1 to 1:4) of CAI with improved efficacy that is relevant to bioavailability and depends on solvability in human body fluids, and another objective is to develop a safer method with better cost performance for production of CAI, CTO, and CAO in bulk, and an important objective is to produce safer CAI by using safe ingredients with low toxicity, instead of using sodium azide or potassium azide that are highly toxic at very small concentration, for producing intermediates, and the invention of the present application made it possible to produce novel polymorphs of CAI and orotic acid formulations thereof and provided a safer method to prepare them.

Accordingly, it is recognized that the problem to be solved by the Amended

Invention that is an invention that relates to polymorphs is to provide novel polymorphs of orotate of CAI to be used in orotic acid formulations (the ratio of base to acid is within the range of 1:1 to 1:4) of CAI with improved efficacy that is relevant to bioavailability and depends on solvability in human body fluids.

D Comparison between/judgment on inventions described in the detailed description of the invention and the Amended Invention

It is examined whether the Amended Invention is identical with the invention described in the detailed description of the invention, whether the invention is within the scope in which a person skilled in the art can recognize that the problem to be solved by the Amended Invention can be solved with descriptions or suggestions in the detailed description of the invention, and whether the invention is within the scope in which a person skilled in the art can recognize that the problem to be solved by the invention can be solved in the light of common technical knowledge as of the time of filing the application even without the descriptions or the suggestion.

As examined with respect to the enablement requirement in above (2), it cannot be deemed that a person skilled in the art can produce polymorphs of the Amended Invention based on descriptions or suggestions in the detailed description of the invention and common technical knowledge as of the time of filing the application.

As far as it cannot be deemed that polymorphs of the Amended Invention can be produced, it cannot be deemed that the problem to be solved by the Amended Invention as shown in above C can be solved.

Accordingly, it cannot be recognized that the Amended Invention is identical with the invention described in the detailed description of the invention and is within the scope in which a person skilled in the art can recognize that the problem to be solved by the Amended Invention can be solved with descriptions or suggestions in the detailed description of the invention, and it also cannot be recognized that the invention is within the scope in which a person skilled in the art can recognize that the problem to be solved by the invention can be solved in the light of common technical knowledge as of the time of filing the application even without the descriptions or the suggestion.

E Summary

As explained above, the Amended Invention is such that the invention for which a patent is sought is not identical with the invention described in the detailed description of the invention, and the recitation in the scope of claims of this application does not comply with the provisions of Article 36(6)(i) of the Patent Act.

(4) Summary for suitability of amendment

Because, as explained above, with respect to the Amended Invention, since the description in the detailed description of the invention in this application does not comply with the provisions of Article 36(4)(i) of the Patent Act, the requirement provided for in Article 36(4)(i) of the Patent Act is not satisfied, and, in addition, since the recitation in the scope of claims does not comply with the provisions in Article 36(6)(i) of the Patent Act, the requirement provided for in Article 36(6) of the Patent Act is not satisfied.

Accordingly, the Amended Invention cannot be independently patentable at the time of filing the application.

3. Closing on the Amendment

Accordingly, since the Amendment violates the provisions of Article 126(7) of the Patent Act applied mutatis mutandis by Article 17-2(6) of the Patent Act, the Amendment should be dismissed under the provisions of Article 53(1) of the Patent Act applied mutatis mutandis pursuant to Article 159(1) of the Patent Act.

Therefore, the appeal decision shall be made as described in [Conclusion of Decision to Dismiss Amendment].

No. 3 Regarding the Invention

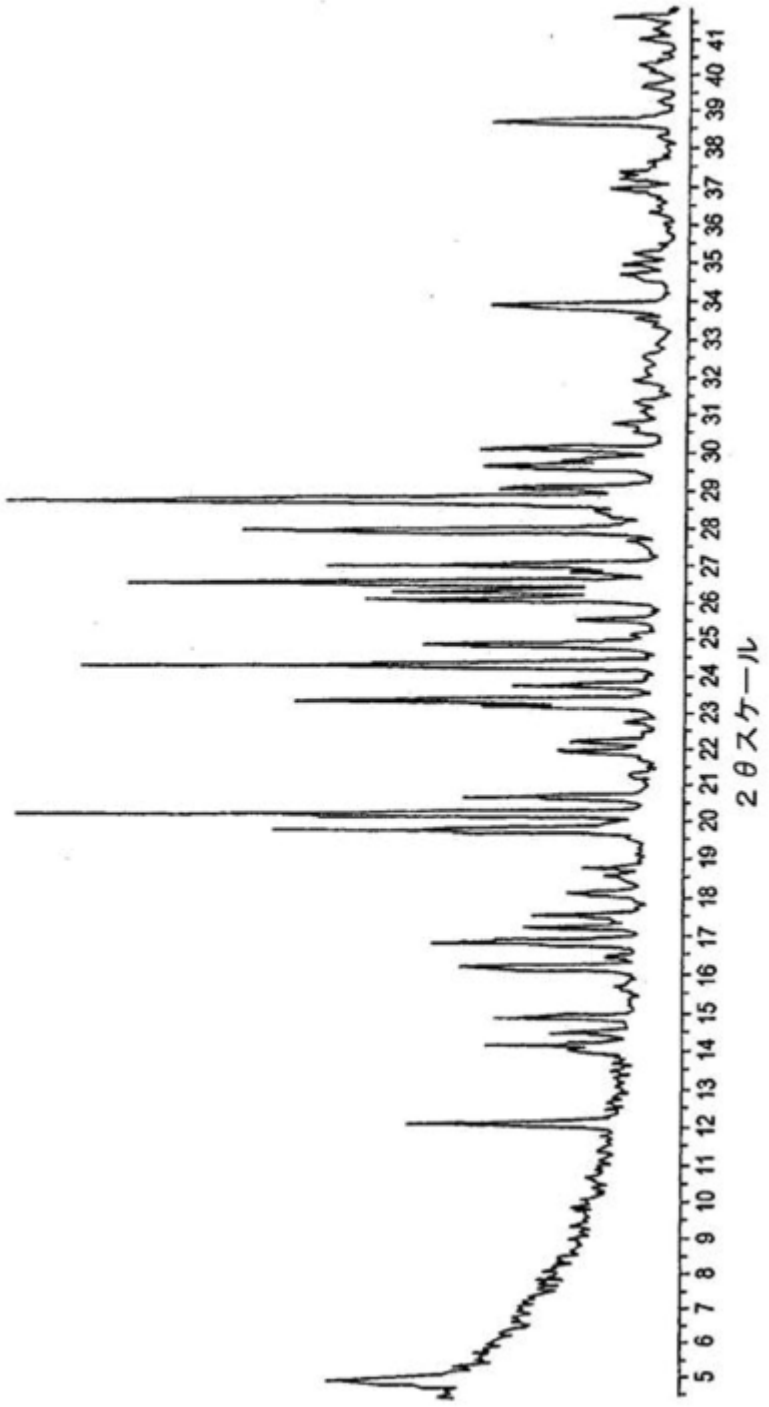
1. The Invention

As the amendment made with the written amendment filed on January 31, 2020 has been dismissed as described above, it is recognized that inventions according to Claims 1 to 10 of the present application are as specified by matters recited in Claims 1 to 10 amended by the written amendment filed on September 4, 2017, and the invention according to Claim 1 (hereinafter, referred to as the "Invention") is as shown below.

"A Form 1 polymorph of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxysamide bonded to orotic acid characterized by an X-ray diffraction pattern substantially shown in FIG. 3, wherein the ratio of base to acid is in the range of 1:1 to 1:4.

FIG. 3

[Chemical 1]



２θスケール　　2θ scale

"

2 Reasons for refusal stated in the examiner's decision

The reasons for refusal stated in the examiner's decision are Reasons 1 to 4 in the notification of reasons for refusal dated October 11, 2018, and Reason 1 is that "(Enablement requirement) The description in the detailed description of the invention of this application does not satisfy the requirement provided for in Article 36(4)(i) of the Patent Act in the following points," and Reason 2 is that "(Support requirement) The recitation in the scope of claims of this application does not satisfy the requirement provided for in Article 36(6)(i) of the Patent Act in the following points."

To be specific, after pointing out with respect to Reasons 1 and 2 that:

"The detailed description of the invention and drawings describe that polymorphs of CTO are CAI to which orotic acid is ionically bonded, and Form 1 and Form 2 have melting points described in paragraph 0036 and 1H-NMR spectrums, FT-IR patterns, and X-ray diffraction patterns illustrated in FIGS. 1 to 6.

However, there is no concrete description of how those polymorphs are obtained.

The specification only describes methods for synthesizing CAI itself or orotate itself and does not describe how crystals of Form 1 and Form 2 are obtained.

Even if Examples are referred to, no physical property is specified with respect to CAI (Example 4) and it is not described whether CAI is crystal, and the result of measurement of melting point of CTO by differential scanning calorimetry (Example 5) does not coincide with those described above as Form 1 and Form 2.

Example 5 includes a literal description that a product of '1:1' was obtained, and Example 7 includes a literal description that a product of '0.7:1.3' was obtained, but there is no description that describes how it was ensured that those products are such ones. With respect to the product of Example 5, only the ratio of CAI and orotic acid as materials is described and there is no description of concrete conditions for the experiment, yield, etc. and, with respect to the product of Example 7, there is no description how it was obtained.

In the literature mentioned in paragraph 0005 of the specification as prior art (Cited Document 2), there is a description that crystals of orotate were obtained, and, in working examples, it is described that, same as in Example 5 of the present specification, notwithstanding that CAI and orotic acid were mixed at the mole ratio 1:1 in methanol/water, ionic crystal of 2:1 was obtained with a high yield of 95% in terms of CAI. Then, even if prior art is taken into consideration, it cannot be deemed that it is self-evident to a person skilled in the art from the description of concrete example described in the present specification, how compounds of not conventional 2:1 but 1:1 and 0.7:1.3, or compounds of 1:1 to 1.4 can be obtained."

The notification of reasons for refusal further points out with respect to Reason 1 that:

"Thus, the detailed description of the invention is not described so that polymorphs of the invention according to Claims 1 to 8, and 'Form 1 polymorph' or 'Form 2 polymorph' of pharmaceutical compositions of the inventions according to Claims 9 to 10 can be produced and used.

Accordingly, the detailed description of the invention of this application is not described sufficiently clear and complete so that a person skilled in the art can work the inventions according to Claims 1 to 10," and, further, with respect to Reason 2, the notification of reasons for refusal points out that:

"Thus, even if the description in the specification and prior art are taken into consideration, it cannot be deemed that a person skilled in the art can understand the means for obtaining 'polymorphs' of inventions according to Claims 1 to 8, and 'Form 1 polymorph' or 'Form 2 polymorph' of pharmaceutical compositions of the inventions according to Claims 9 to 10.

Therefore, the inventions according to Claims 1 to 10 are not identical with inventions described in the detailed description of the invention."

In the examiner's decision and the notification of reasons for refusal, it is described as "2. National Publication of International Patent Application No. H11-510141" in the "List of Cited Documents, etc."

The Invention is an invention according to Claim 1 referred to in the notification of reasons for refusal.

3 Judgment by the body

In the Invention, since the matter specifying the invention, "an X-ray diffraction pattern substantially shown in FIG. 3" substitutes for the matter specifying the invention, "an X-ray diffraction pattern shown in FIG. 3" in the above Amended Invention just by adding a word, "substantially" and the Invention covers inventions without the matter specifying the invention, "substantially," the Invention is an invention that includes the Amended Invention.

No amendment of the detailed description of the invention and drawings has been made for the present application.

Then, as stated in Part 2 [Reason], 2, with respect to the Amended Invention, since the description in the detailed description of the invention does not comply with the provisions of Article 36(4)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(4)(i) of the Patent Act and, since the

recitation in the scope of claims does not comply with the provisions of Article 36(6)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(6) of the Patent Act. Therefore, also with respect to the Invention that covers the Amended Invention, due to the same reasons, since the description in the detailed description of the invention does not comply with the provisions of Article 36(4)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(4)(i) of the Patent Act, and, since the description in the scope of claims does not comply with the provisions of Article 36(6)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(6) of the Patent Act.

No. 4 Closing

As explained above, with respect to the Invention, since the description in the detailed description of the invention does not comply with the provisions of Article 36(4)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(4)(i) of the Patent Act, and, since the description in the scope of claims does not comply with the provisions of Article 36(6)(i) of the Patent Act, the present application does not satisfy the requirement provided for in Article 36(6) of the Patent Act.

Accordingly, the present application should be rejected without examining other matters.

Therefore, the appeal decision shall be made as described in the conclusion.

January 8, 2021

Chief administrative judge: MURAKAMI, Kimitaka
Administrative judge: SAITO, Mayumi
Administrative judge: TOMINAGA, Tamotsu