Appeal decision

Appeal No. 2016-15132

U.S.A.

Appellant	Merck Sharp & Dohme Corporation
Patent Attorney	ONO Makoto
Patent Attorney	KANAYAMA Masakata
Patent Attorney	TSUBOKURA Michiaki
Patent Attorney	SHIGEMORI Kazuki
Patent Attorney	ANDO Kenshi
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U.K.

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Patent Attorney SHIROYAMA Yasufumi

The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2014-518879, titled "Novel crystalline forms of dipeptidyl peptidase-IV inhibitor" (International Publication, January 3, 2013, WO2013/003249; National Publication, July 28, 2014, No. 2014-518266) has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

This application was filed on June 25, 2012 (claim of priority under the Paris Convention was received by the foreign receiving office, June 29, 2011 (US)), a written amendment was submitted on April 2, 2015, the reasons for refusal were notified on October 8, 2015, a written opinion and a written amendment were submitted on January 18, 2016, a decision for refusal was made on June 8, 2016, and an appeal against the examiner's decision of refusal was made on October 7, 2016 and a written amendment was submitted at the same time.

A divisional application of a part of this application was filed on October 7, 2016 as Japanese Patent Application No. 2016-198829.

No. 2 Decision to dismiss amendment in the written amendment dated October 7, 2016

[Conclusion of Decision to Dismiss Amendment]

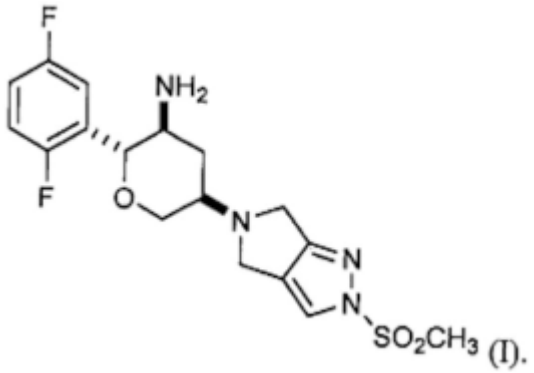
The amendment dated October 7, 2016 is dismissed.

[Reason]

1 Amendment

The amendment of October 7, 2016 (hereinafter, referred to as "the Amendment") was an amendment to modify Claim 1 before the amendment, "a crystalline substance (2R, 3S, 5R)-2-(2, 5-Difluorophenyl)-5-[2-(methyl sulfonyl)-2, 6-dihydropyrrolo[3,4-c] pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine (Form I) of compound I, having at least four peaks selected from a group consisting of 10.3 ± 0.1 2θ,

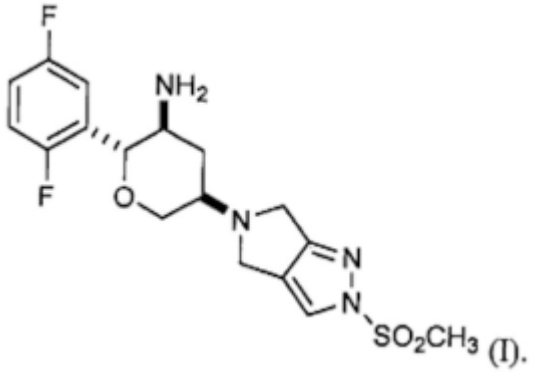
12.7 ± 0.1 2θ, 14.6 ± 0.1 2θ, 16.1 ± 0.1 2θ, 17.8 ± 0.1 2θ, 19.2 ± 0.1 2θ, 22.2 ± 0.1 2θ, 24.1 ± 0.1 2θ, and 26.9 ± 0.1 2θ in its powder X-ray diffraction pattern



(I).

" to

"a crystalline substance (2R, 3S, 5R) -2- (2, 5-Difluorophenyl) -5- [2- (methylsulfonyl) -2, 6- dihydropyrrolo [3, 4-c] pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine (Form I) of compound I, having at least four peaks selected from a group consisting of 10.3 ± 0.1 2θ, 12.7 ± 0.1 2θ, 14.6 ± 0.1 2θ, 16.1 ± 0.1 2θ, 17.8 ± 0.1 2θ, 19.2 ± 0.1 2θ, 22.2 ± 0.1 2θ, 24.1 ± 0.1 2θ, and 26.9 ± 0.1 2θ in the powder X-ray diffraction pattern,



(I).

and, the crystal form of Form I is more stable in powder X-ray diffraction in isopropyl acetate at 25°C than the crystal form of Form II,

wherein,

the crystal form of Form II has at least four peaks selected from a group consisting of 7.5 ± 0.1 2θ, 15.0 ± 0.1 2θ, 16.2 ± 0.1 2θ, 20.9 ± 0.1 2θ, 22.0 ± 0.1 2θ, 27.0 ± 0.1 2θ, 27.6 ± 0.1 2θ, and 33.3 ± 0.1 2θ in its powder X-ray diffraction pattern"

(Remark by the appeal decision: Amended portions were underlined).

2 Propriety of amendment

Difference between Claim 1 before the amendment and Claim 1 after the amendment is examined below.

According to the description in the detailed description of the invention, the

matter added by the amendment, "and, the crystal form of Form I is more stable in powder X-ray diffraction in isopropyl acetate at 25°C than the crystal form of Form II, wherein,
the crystal form of Form II has at least four peaks selected from a group consisting of 7.5 ± 0.1 2θ, 15.0 ± 0.1 2θ, 16.2 ± 0.1 2θ, 20.9 ± 0.1 2θ, 22.0 ± 0.1 2θ, 27.0 ± 0.1 2θ, 27.6 ± 0.1 2θ, and 33.3 ± 0.1 2θ in its powder X-ray diffraction pattern," represents properties originally exhibited by the crystalline substance, (2R, 3S, 5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2, 6-dihydropyrrolo [3, 4-c] pyrazole- 5(4H)-yl] tetrahydro-2H-pyran -3-amine (Form I) specified by groups of numerical values of 2θ in a specific powder X-ray diffraction pattern of the invention described in Claim 1 before the amendment, and is not such that, before the amendment, there were some having such property and the others not having such property and it is specified to the former. Accordingly, the range of the crystalline substance specified by a group of numerical values of 2θ of specific powder X-ray diffraction pattern (2R, 3S, 5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl) -2, 6 -dihydropyrrolo [3,4-c] pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine (Form I) described in Claim 1 does not vary between before the amendment and after the amendment.

Then, since amendment to change Claim 1 before the amendment to Claim 1 after the amendment does not restrict matters necessary for specifying the Invention described in the scope of claims, the Amendment is not to aim at the restriction of the scope of claims stipulated in Article 17-2(5)(ii) of the Patent Act. In addition, the Amendment does not fall under cancellation of a claim or claims stipulated in Article 17-2(5)(i), the correction of errors stipulated in Article 17-2(5)(iii), or the clarification of an ambiguous statement stipulated in Article 17-2(5)(iv).

The invention according to Claim 5 before the amendment was an invention related to a crystalline substance (2R,3S,5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2, 6-dihydropyrrolo [3, 4-c] pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine (Form I), the inventions according to Claims 2 to 4 and 6 to 8 were inventions related to crystal form, the invention according to Claim 9 before the amendment was an invention related to the use of crystal form in manufacture of pharmaceuticals, and the inventions according to Claims 10 to 12 before the amendment were inventions related to pharmaceutical compositions, and, even if the relationship between Claim 1 after the amendment and Claims 2 to 12 before the amendment is examined, the Amendment does not fall under any of Article 17-2(5)(i) to (iv).

3 Closing

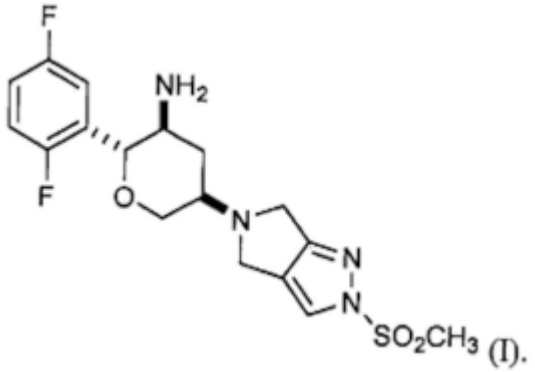
As mentioned above, the Amendment violates the provisions of Article 17-2(5) of the Patent Act, and thus should be dismissed under the provisions of Article 53(1) of the same Act which is applied mutatis mutandis pursuant to Article 159(1) of the same Act.

Therefore, it is decided as described in the above mentioned [Conclusion of Decision to Dismiss Amendment].

No. 3 The Invention

Since the amendment dated October 7, 2016 was dismissed as described above, the invention of the application should be specified with the matters described in Claims 1 to 12 in the scope of claims amended by the amendment of January 18, 2016, and the invention according to Claim 1 (hereinafter, referred to as "the Invention") is as shown below.

"A crystalline substance (2R, 3S, 5R)-2- (2, 5-difluorophenyl)-5-[2-(methylsulfonyl)-2, 6-dihydropyrrolo [3, 4-c] pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine (Form I) of compound I, having at least four peaks selected from a group consisting of 10.3 ± 0.1 2θ, 12.7 ± 0.1 2θ, 14.6 ± 0.1 2θ, 16.1 ± 0.1 2θ, 17.8 ± 0.1 2θ, 19.2 ± 0.1 2θ, 22.2 ± 0.1 2θ, 24.1 ± 0.1 2θ and 26.9 ± 0.1 2θ in its powder X-ray diffraction pattern (Form I)



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No. 4 Reasons for refusal stated in the examiner's decision

The reason for refusal is Reason 2 in the notification of reasons for refusal dated October 8, 2015, and, roughly speaking, since inventions according to Claims 1 to 20 of the application could have been easily invented by a person skilled in the art based on inventions disclosed in Cited Documents No.1 to No.7 distributed before the filing and common technical knowledge, the appellant should not be granted a patent for the Invention in accordance with the provisions of Article 29(2) of the Patent Act. Cited

Document 1 is international publication No. 22010/056708 (hereinafter, referred to as "Publication 1"), Cited Document 2 is "Pharmaceutical Polymorphism and Crystallization" by Kazuhide Ashizawa as author and editor, Maruzen Planet Co., Ltd., September 20, 2002, pages 3 to 16 (hereinafter, referred to as "Publication 2"), Cited Document 3 is "Pharmacy - Basics and Applications," Nanzando, September 20, 1977, pages 142 to 145 (hereinafter, referred to as "Publication 3"), Cited Document 4 is "New Pharmacology," Nanzando, April 25, 1984, pages 102 to 103, and 232 to 233 (hereinafter, referred to as "Publication 4"), Cited Document 5 is "New Pharmacology, General Theory (revised edition, third printing)," Nankodo, April 10, 1987, page 111 (hereinafter, referred to "Publication 5"), Cited Document 6 is "Experimental Chemistry (sequel) 2 Isolation and Purification," Maruzen, January 25, 1967, pages 159 to 178 and 186 to 187 (hereinafter, referred to as "Publication 6"), and Cited Document 7 is International Journal of Pharmaceutics, 283, 2004, pages 117 to 125 (hereinafter, referred to as "Publication 7"). The Invention corresponds to the invention according to Claim 2 referred to in the notification of reasons for refusal.

No. 5 Judgment by the body

The body judges that, as reasoned in examiner's decision, since the Invention could have been easily invented by a person skilled in the art based on inventions disclosed in Publications 1 to 7 and common technical knowledge, the Invention should not be granted a patent in accordance with the provisions of Article 29(2) of the Patent Act.

Reasons are as follows:

1 Publications

Publication 1: International publication No. 2010/056708 (Cited Document 1 in the original examination)

Publication 2: "Pharmaceutical Polymorphism and Crystallization" by Kazuhide Ashizawa as author and editor, Maruzen Planet Co., Ltd, September 20, 2002, pages 3 to 16 (Cited Document 2 in the original examination)

Publication 3: "Pharmacy - Basics and Applications," by Sadao Nishigaki, 3rd printing, Nanzando, September 20, 1977, pages 142 to 145 (Cited Document 3 in the original examination)

Publication 4: "New Pharmacology," edited by Yoshinobu Nakai, and Manabu Hanai, 2nd printing, Nanzando, April 25, 1984, pages 102 to 103, and 232 to 233 (Cited Document 4 in the original examination)

Publication 5: "New Pharmacology, General Theory (revised edition, third printing)," by Jo Okano as author and editor, Nankodo, April 10, 1987, page 111 (Cited Document 5 in the original examination)
Publication 6: "Experimental Chemistry (sequel) 2 Isolation and Purification," edited by the Chemical Society of Japan, Maruzen Co., Ltd., January 25, 1967, pages 159 to 178 and 186 to 187 (Cited Document 6 in the original examination)
Publication 7: International Journal of Pharmaceutics, 283, 2004, pages 117 to 125 (Cited Document 7 in the original examination)
Publication 8: "Iwanami Dictionary of Physics and Chemistry, 5th edition" edited by Sabro Hasekura, Hiroo Iguchi, Hiroshi Ezawa, Shu Iwamura, Fumitaka Sato, and Ryogo Kubo, 5th edition, 8th printing, December 20, 2004, Iwanami Shoten, Publishers, page 504
Publication 9: "Experimental Chemistry, 4th edition, Basic Operation I" edited by the Chemical Association of Japan, 2nd printing, Maruzen Co., Ltd., April 5, 1996, pages 184 to 186
Publication 10: Pharmaceutical Research, 12 (7), 1995, pages 945 to 954 (Evidence A No. 5 submitted in the trial for invalidation to Japanese Patent No. 4790194 corresponding to Publication 12 (Muko No. 2013-800037 (hereinafter, referred to as "trial for invalidation for Atorvastatin")); document in hand of the body' is marked as "Exhibit A No. 5" and "Demand for trial for invalidation No. 13-000351" Evidence A No. 5" and "Demand for trial for invalidation" and accompanied by excerpt)
Publication 11: Japanese Unexamined Patent Application Publication No. 6-192228
Publication 12: Japanese Unexamined Patent Application Publication No. 2003-73353
Publication 13: Chemistry & Industry, 21, 1989, pages 527 to 529 (Evidence A No. 8 submitted in the trial for invalidation for Atorvastatin; document in hand of the body is marked as "Exhibit A No. 8" and "Demand for trial for invalidation No. 13-000354" and accompanied by excerpt)

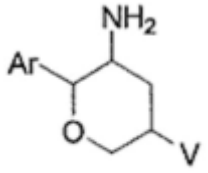
Publications 8 to 13 are cited in addition to Publications 2 to 7 cited in the original examination in order to indicate common technical knowledge.

2 Described matters in Publications

A Publication 1

Translation is shown below.

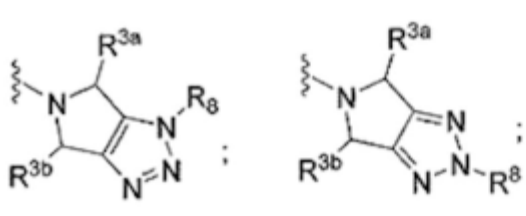
(1a) "1. A compound of structural formula I:

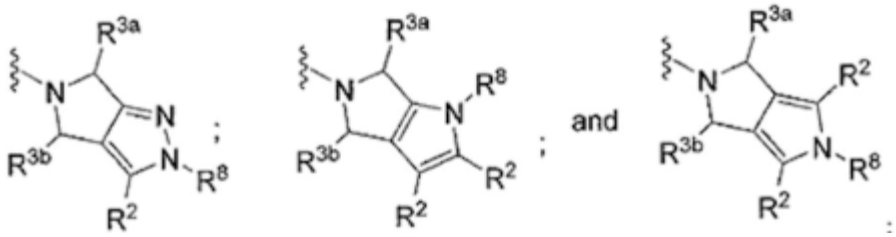


(I)

or a pharmaceutically acceptable salt thereof, wherein

V is selected from the group consisting of





and

:

Ar is phenyl optionally substituted with one to five R1 substituents;

each R1 is independently selected from the group consisting of halogens ...;

each R2 is independently selected from the group consisting of hydrogen ...;

R3a and R3b are respectively independently hydrogen or ...;

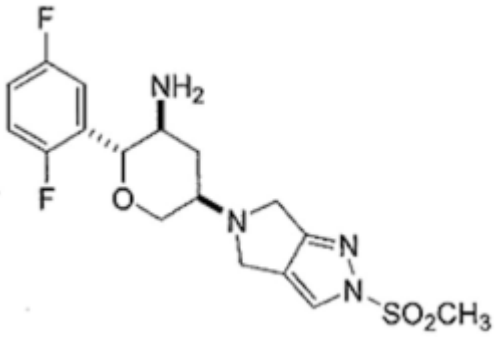
.....

R8 is selected from a group consisting of -SO2C1-6 alkyl ...

.....

18.

A compound selected from the group consisting of



.....

or pharmaceutically acceptable salt thereof" (pages 60 to 67, Claims 1 and 18 in the

Scope of Claims)

(1b) "Field of the invention

The present invention relates to novel substituted aminotetrahydropyrans which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DPP-4 inhibitor") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

Background of the invention

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein, and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore, patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism, and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In Type 2 diabetes or noninsulin dependent diabetes mellitus, (NIDDM) patients often have plasma insulin levels that are the same or even elevated compared to non-diabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver, and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

.....

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DPP-4") enzyme have also been found useful for the treatment of diabetes, particularly Type 2 diabetes ...

.....

SUMMARY OF THE INVENTION

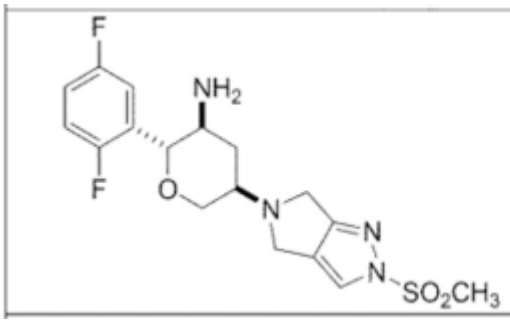
The present invention is directed to novel substitutes 3-aminotetrahydropyrans which as inhibitors of the dipeptidyl peptidase-IV enzyme ("DPP-4 inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved" (page 1, line 5 to page 4, line 22).

(1c) "Nonlimiting examples of compounds of the present invention that are useful as dipeptidyl peptidase-IV inhibitors are the following structures having the indicated absolute stereochemical configurations at the three stereogenic tetrahydropyran carbon atoms:

実施例	IC_{50} DPP-4 阻害

実施例 Example
阻害 Inhibition

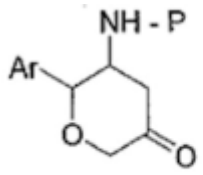
.....

	2.5 nM

.....

and a pharmaceutically acceptable salt thereof" (page 11, line 18 to page 13, line 1).

(1d) "The compounds of the present invention can be prepared from intermediates such as those of formula II and III using standard reductive amination conditions followed by deprotection.

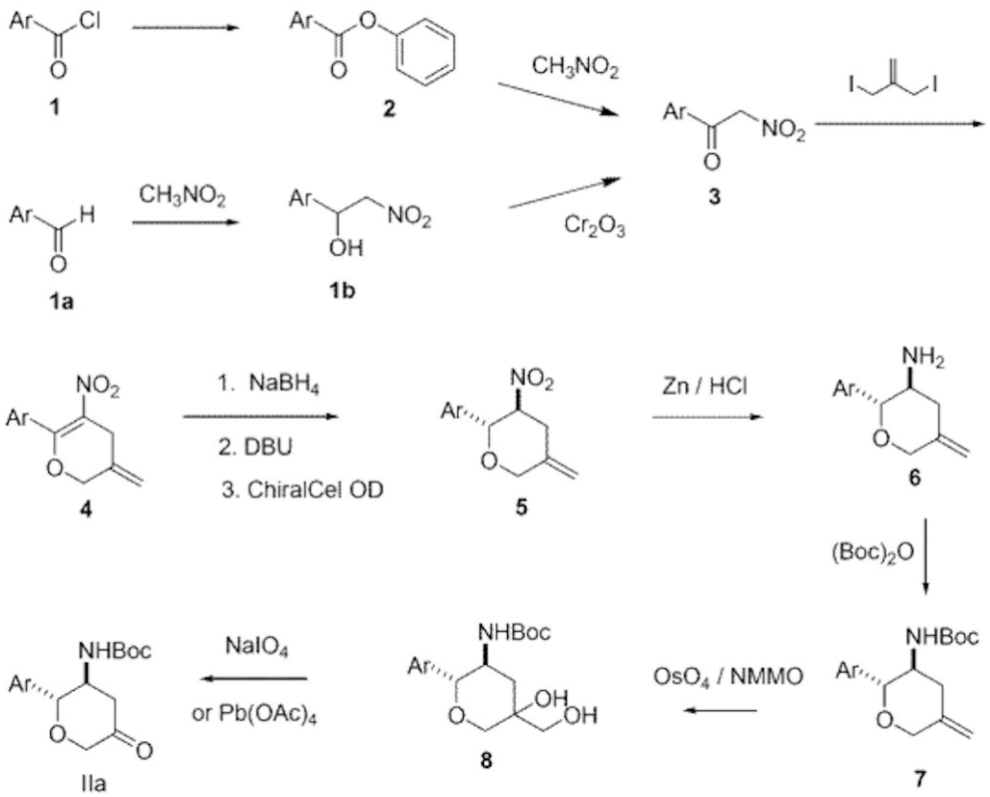


II

III

Where Ar and V are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), or 9-fluorenylmethoxycarbonyl (Fmoc). The preparation of these intermediates is described in the following Schemes.

スキーム 1

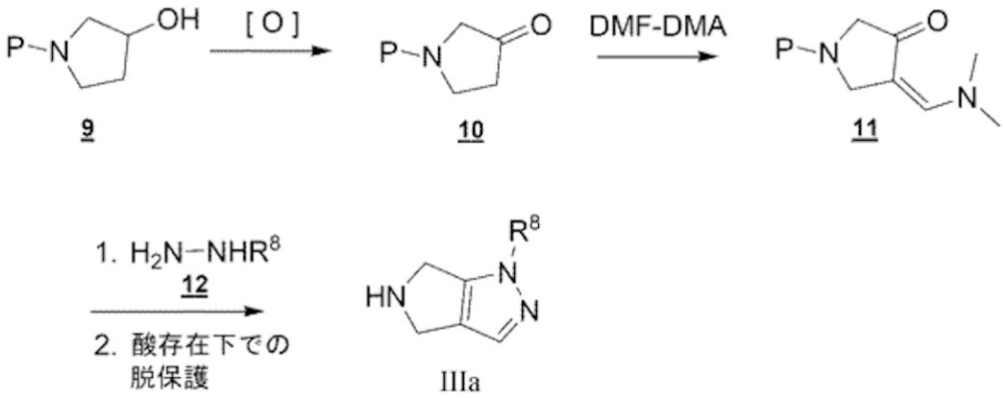


スキーム 1　　SCHEME 1

Intermediates of formula II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Substituted benzoyl halide 1 is treated with phenol in the presence of a base such as N, N-diisopropylethylamine to form the ester 2. Treatment of the ester 2 with the anion generated from nitromethane using sodium

hydride gives the nitroketone 3. Alternatively, the nitroketone 3 can be made by reacting aldehyde 1a with nitromethane in the presence of a base and oxidizing the resulting nitroalcohol 1b with an oxidizing agent such as Jones reagent. Heating the nitroketone 3 with 3-iodo-2-(iodomethyl)prop-1-ene gives the pyran 4, which, when reduced with sodium borohydride and isomerized with a base such as 1, 8-diazabiyclo[5.4.0]undec-7-ene (DBU), provides the trans pyran 5. The enantiomers of 5 may be separated at this stage by a variety of methods known to those skilled in the art. Conveniently, the racemate may be resolved by HPLC using a chiral column. The-nitro-substituted pyran 5 is then reduced, for example, using zinc and an acid, such as hydrochloric acid, and the resulting amine 6 is protected, for example, as its BOC derivative, by treatment with di-tert-butyl decarbonate to give 7. Treatment of 7 with osmium tetroxide and N-methylmorpholine N-oxide forms the diol 8 which upon treatment with sodium periodate gives intermediate pyranone IIa.

スキーム 2

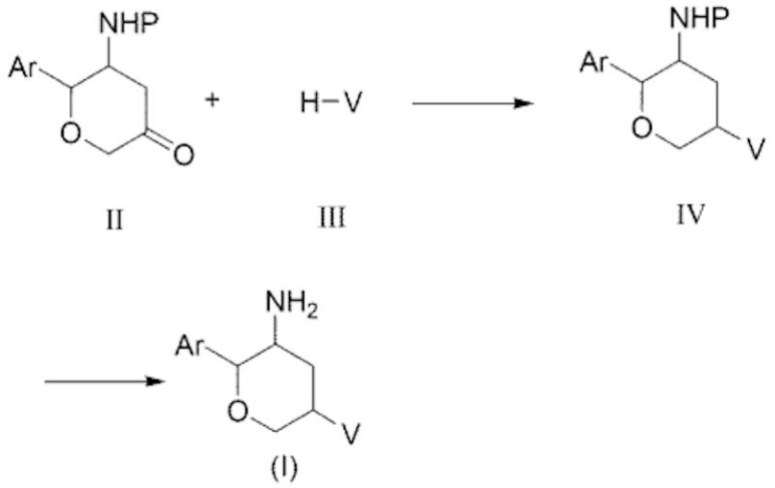


スキーム 2　　SCHEME 2

酸存在下での脱保護　　Deprotection with acid

Intermediates of formula III are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route to prepare tetrahydropyrrolopyrazole IIIa is illustrated in Scheme 2. Trityl- or Boc-protected pyrrolidinol 9 may be oxidized by a variety of methods, such as the Swern procedure, commonly known to those in the art, to give the ketone 10, which upon treatment and heating with N, N-dimethylformamide dimethyl acetal (DMF-DMA) gives 11. The desired intermediate IIIa may then be readily obtained by heating a solution of 11 with hydrazine 12 in a suitable solvent such as ethanol optionally in the presence of a base such as sodium ethoxide followed by removal of the protecting group with acid.

スキーム 3



スキーム 3　　SCHEME 3

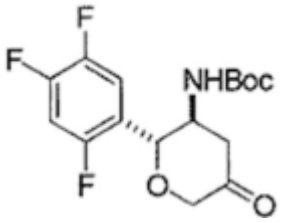
As illustrated Scheme 3, the compounds of the present invention structural formula (I) may be prepared by reductive animation of Intermediate II in the presence of Intermediate III using reagents such as sodium cyanoborohydride, decaborane, or sodium triacetoxyborohydride in solvents such as dichloromethane, tetrahydrofuran, or methanol to provide Intermediate IV. The reaction may also be facilitated by adding an acid such as acetic acid. In some cases, Intermediate III may be a salt, such as a hydrochloric acid or trifluoroacetic acid salt, and in these cases, it is convenient to add a base, generally N, N-diisopropylethylamine, to the reaction mixture. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc or palladium-on-carbon and hydrogen gas in the case of Cbz to give the desired amine I. The product is purified, if necessary, by recrystallization, trituration, preparative thin layer chromatography, or flash chromatography on silica gel, such as with a Biotage® apparatus or HPLC. Compounds that are purified by HPLC may be isolated as the corresponding salt.

In some cases, the product I or synthetic intermediate illustrated in the above schemes may be further modified, for example, by manipulation of substituents on Ar or V. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions that are commonly known to those skilled in the art. In some cases, the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The compound of structural formula I of the present invention can be prepared

according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples. ... The Examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts such as those described previously hereinabove. The free amine bases corresponding to the isolated salt can be generated by neutralization of a suitable base such as aqueous sodium hydrogen carbonate, sodium carbonate, sodium hydroxide, or potassium hydroxide, and extraction of the liberated amine free base into an organic solvent followed by evaporation. The amine free base isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid and subsequent evaporation, precipitation, or crystallization. ..." (page 38, line 1 to page 41, line 13).

(1e) "Intermediate 1



tert-Butyl [2R, 3S]-5-oxo-e-(2, 4, 5-trifluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate

Step A: Phenyl 2, 4, 5-trifluorobenzoate

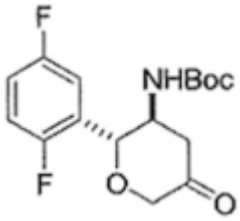
A solution of phenol ... in dry dichloromethane ... was cooled in an ice bath and treated with N, N-diisopropylethylamine ... followed by dropwise addition of 2, 4, 5-trifluorobenzoyl chloride over a period of 15 minutes. The organic layer was ...evaporated, and the resulting solid product was ... purified on silica ... as white solid.

.....

Step H: tert-Butyl [(2R, 3S)-5-oxo-2-(2, 4, 5 trifluorophenyl)tetrahydro 2H-pyran-3-yl]carbamate

... purified by flash chromatography to yield ... as white solid.

Intermediate 2



tert-Butyl [(2R, 3S)-5-oxo-2-(2, 5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate

Step A: 1-(2, 5-Difluorophenyl)-2-nitroethanol

... sodium hydroxide (1N, ...) and methanol ... 2, 5-difluorobenzaldehyde ... and nitromethane ... in methanol ... dropwise over a period of 1 h. ... neutralized with glacial acetic acid ... Diethyl ether was added, and the layers separated. ... The organized layer was ... concentrated ... used without further purification in Step B.

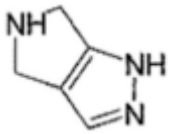
.....

... made by following the same method described in Intermediate 1...

Step I: tert-Butyl[(2R, 3S)-5-oxo-2-(2, 5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate

... purified by chromatography ... to yield ... as white solid" (page 42, line 12 to page 47, line 2).

(1f) "Intermediate 3



Step A: tert-Butyl(3Z)-3-[(dimethylamino)methylene]-4-oxopyrrolidine-1-carboxylate

A solution of tert-butyl3-oxophrrolidine-1-carboxylate ... was treated with DMF-DMA ... resulting orange solid was treated ... cooled ... The resulting brownish-yellow solid obtained ... was collected by filtration, dried, and used in the next step without further purification.

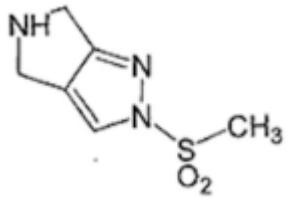
Step B: 1, 4, 5, 6-tetrahydropyrrolo[3,4c] pyrazole

A solution of hydrazine ... tert-butyl(3Z)-3-[(dimethylamino)methylene]-4-oxopyrrolidine-1-carboxylate ... in ethanol ... was heated at 85°C in a sealed tube for 4h. Solvent was removed under reduced pressure, and the residue was triturated with dichloromethane ... and ethyl acetate. The resulting solid was filtered. The filtrate was concentrated and the resulting solid was triturated again and filtered. The combined solids were treated with 4N hydrochloric acid in methanol ...purified ... to

yield ... 1,4,5,6-tetrahydropyurrolo[3,4-c]pyrazole.

.....

Intermediate 5



2-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole

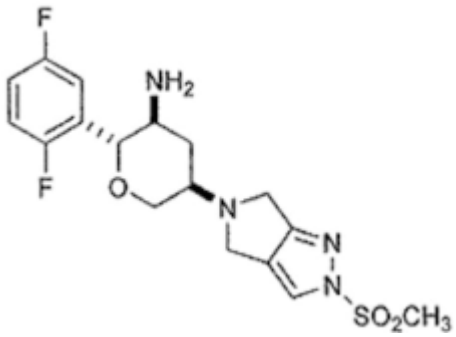
Step A: tert-Butyl 1-(methylsulfonyl)]4,6-dihydropyrrolo[3,4-c]pyrazole5(1H)-carboxylate (A) and tert-buryol 2-(methylsulfonyl)]-2,6-dihydropyrrolo[3m4-c]pyrazole-5(4H)-carboxylate (B)

A suspension of N-Boc-pyrazolopyrolidine (Intermediate 3, Step B) ... in anhydrous acetonitrile ... was charged in a 2.0 L three-neck flask fitted with a thermometer and an addition funnel and then treated with sodium hydride... while under nitrogen atmosphere in one portion. ... The resulting white suspension was then cooled in an ice bath and methanesulfonyl chloride was slowly added via an addition funnel. ... stirred at room temperature for 1h ... the reaction of the reaction mixture is stopped using ... water ..., the layers were separated. ...The aqueous layer was then extracted with ... dichloromethane ... The combined organic layers were dried over sodium sulfate and concentrated ... to give a mixture of products A and B as colorless syrups. NMR ... indicated a 1:1 mixture of two products, ...

Step B: 2-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,4c]pyrazole

... desired Intermediate 5 was obtained in dichloromethane... after chromatography by Biotage™ column ... eluted with 2.5-12.5% methanol and 0.25-1.25% ammonium hydroxide in dichloromethane..." (page 47, line 3 to page 49, line 28).

(1g) "Example 1



(2R,3S,5R)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-

c]pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine

Step A: tert-Butyl{(2R,3S,5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-yl]tetrahydro-2H-pyran-3-yl}carbamate

A mixture of Intermediate 2 (26.3 g, 80 mmol) and 2-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (Intermediate 5) (15.07 g, 80 mmol) in anhydrous methanol (1.5 L) was stirred at room temperature for 2 h. To the resulting white suspension was added decaborane (2.95 g, 24.15 mmol) and the mixture was stirred at room temperature overnight. Methanol was removed and the residue was purified on two 65i Biotage™ columns eluting with 5-50% ethyl acetate in dichloromethane to afford the title compound as a white solid.LC - MS: 499.10 (M+1).

Step B: (2R,3S,5R)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-yl] tetrahydro-2H-pyran-3-amine

Removal of the BOC group in the product from Step A (13.78 g, 27.67 mmol) was accomplished with trifluoroacetic acid (100 mL) at room temperature. After stirring for 2 h, the reaction was concentrated and neutralized with 25% MeOH and 2.5% ammonium hydroxide in dichloromethane. Solvents were removed under reduced pressure and the resulting crude material was purified on a 65i Biotage™ columns eluting with 1.25 ~ 5% MeOH and 0.125-0.5% ammonium hydride in dichloromethane. The isolated material was further purified by recrystallization from 5:1 EtOAc/CH2Cl2 at 60 °C. The crystalline product was washed with cold 2:1 EtOAc/hexanes to give the title compound as a light brown solid. 1H NMR (500 MHz, CD3OD): 1.71 (q, 1H, J = 12 Hz), 2.56 - 2.61 (m, 1H), 3.11 - 3.18 (m, 1H), 3.36 - 3.40 (m, 1H), 3.48 (t, 1H, J = 12 Hz), 3,88- 3.94 (m, 4), 4.30 - 4.35 (m, 1H), 4.53 (d, 1H, J = 12 Hz), 7.14 - 7.223 (m, 2H), 7.26 - 7.30 (m, 1H), 7.88 (s, 1H). LC - MS: 399.04 (M + 1) (page 50, line 33 to page 51, line 27).

(1h) "EXAMPLE OIF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any one of the Examples, 268 ng microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tables" (page 59, lines 2 to 7).

B Publication 2

(2a) "Although crystal polymorphism is widely observed in solid material science not

limited to drugs, it is a very important item that should be taken into consideration in the field of drugs from viewpoints of efficacy, safety, and quality. Namely, differences in molecular state should be taken into consideration, such as crystal polymorph in solid condition and pseudo-polymorph, difference in crystallinity, interaction between water and excipient affect solubility to water or aqueous solution, and dissolution rate, as should physical and chemical properties such as melting temperature, melting heat, and lattice energy. For example, dosage form destruction and reduced applicability could occur because of crystalline growth caused by polymorph transformation, and, from the viewpoint of the molecular level, it can be imagined that difference in chemical reactivity between polymorph forms is caused by the difference in intermolecular or interatomic distance in the crystal, possibly resulting in difference in chemical stability during storage of active pharmaceutical ingredients and drug products. Accordingly, it is essential for persons who are engaged in material science of studies of drugs to become experts in crystal characteristics such as polymorphism of drugs.

First, it is argued what is a crystal polymorph in drugs. It is said that, because drugs have complicated chemical structures, 70% of solid active ingredients exhibit crystal polymorphs. Halebilan et al., report that 67% of steroids that have a melting point of 210°C or less and 63% of barbituric acids have polymorphs, and many antibiotic substances have polymorphs 3). Summary of polymorphs by Halebilan et al., is shown in Table 1.

表1 Polymorphism of Drugs

Compd.	NO. Studied	% Having Polymorphs	% of Unstable Samples
Steroids (m.p. less than 210°)	48	67	17
Sulfonamides	40	40	23
Barbiturates	38	63	11

a Reprinted from *Pure and Applied Chemistry*, 10, 136 (1965), by permission of the International Union of Pure and Applied Chemistry and Butterworths Scientific Publications.

Crystal polymorphs are defined as identical substances that have different crystal structures, and control of crystal polymorphs is quite important for drugs because crystal polymorphs are involved in various problems such as stability, solubility, and efficacy in vivo. ...

If there are identical substances that differ in crystal structure, such substances are called crystal polymorphs, and it is expressed that such crystal structures have a relationship of polymorphs to each other. There is a somewhat old book written by

Stephen R. Byrn entitled "Solid-State Chemistry of Drugs (1982)" in which crystal polymorphs of sulfonamides and steroids are explained and reports on solid phases having different melting points are summarized 5). The following tables 3, 4 and 5 are excerpts from S, R. Byrn's book. It can be understood that quite a large number of polymorphs exist in drugs.

表3 Polymorphism of Sulfonamides and Related Compounds[a]

Compound	Melting point of form(℃)						
	I	II	III	IV	V	VI	VII
Acetazolamide	258-260	248-250					
Acetylsulfisoxazole	190-195	176-177	173-174				
Chlortalidone	212-224	188-189					
Clofenamide	210-215	203-207	183-185	168-170			
Diphenylmethane-4, 4′-disulfonamide	185-187	172-174					
Mafenide hydrochloride	250-260	235-240	220-225	210-212			
N′-Methyl-*N*⁴-sulfanilylsulfanilamide	148-151	144-146					
Phtalylsulfathiazole	260-274	230					
Sulfachlorpyridazine	196-197	178-181					
Sulfadichramide	176-180	174-176					
Sulfadimidine	206-208	199	178	~175			
Sulfaethidole	188	181	149				
Sulfafurazole	190-195	131-133					
Sulfaguanidine	187-191	174-176	143-145				
Sulfamerizine	235-238	228					
Sulfameline	210-212	197-199	181-183	179-181	176-177	155	
Sulfamethizole	209	193					
Sulfamethaoxazole	169	168	166				
Sulfamethoxypyridazine	180-182	158-159	153-154				
Sulfamoxole	200-204	188-195	177-180				
4′-Sulfamoyl-2, 4-diaminoazobenzeze	224-228	217-219	212				
Sulfanilamide	165	156	153				
N-Sulfanilyl-3, 4-xylamide	215-218	208	203	196			
Sulfapyridine	192	185	179	176	174	167	149
Sulfathiazole	202	175	162	158			
Sulfathiourea	178-180	168-171					
Sulfatriazine	158-166	132-135					
Sulfametoxin	194-198	176-177	156-158				
Tolbutamide	127	117	106				
Vesulong	182-185	176-178					

[a] This table shows the melting points of the polymorphic forms of the various drugs.
(Data from Kuhnert-Brandstatter, 1971)

.....

All crystal polymorphs become the same if they are dissolved, but, with respect to drugs, crystal polymorphs cause a problem if the difference in solubility (including dissolution rate) between crystal polymorphs is large. In such a case, the possibility of influence on absorbability of drugs becomes large. In some cases, a difference in crystal polymorphs causes a difference in physicochemical properties of substances that results in problems in formulation. The largest problem is the possibility of influence

on bioavailability. Namely, solubility and dissolution rate differ due to difference in crystal forms, resulting in difference in absorbability, which affects efficacy. ...

表4 Melting Points of Polymorphic Steroids [a]

Compound	Forms				
	I	II	III	IV	V
Allopregnane-3β, 20α-diol	215-219	162-168			
Allopregnane-3, 20-dione	202-206	198-203			
Androstane-3β, 17β-diol	168-169	163-164	158-161	146-147	
Androstane-3,17-dione	132-134	128-130			
Androstanolone	182	168			
Δ5-Androstene-3β,17α-diol	202-205	180-195			
Δ5-Androstene-3β,17β-diol	181-185	177-180	155-158		
Δ4-Androstene-3,17-dione	170-174	142-145			
Corticosterone	180-186	175-179	162-168	155-160	
Cortisone enanthate	138-140	135-137	129-132		
Dehydroepiandrosterone	149-153	139-141	137-140	130-136	
Dehydroepiandrosterone acetate	170-172	132-135	94-96	65-69	
Epiandosterone	174-176	167-169			
Etiocholane-3α-ol-17-one	150-152	141-143	133		
Etiocholane-17β-ol-3-one	141-143	103			
Fluorocortisone trimethylacetate	192-198	184-190			
9α-Fluorohydrocortisone acetate	225-233	208-212	205-208		
Hydrocortisone hemisuccinate	198-205	182-188	168-172		
Methandriol	205-208	202-205	196-198		
Methandriol dipropionate	83-86	74-75			
17α-Methandrostane-3β,17β-diol	213	205			
1-Methylandrostenolone acetate	143	106			
17α-Methylestradiol	190-194	188			
6-α-Methylprednisolone acetate	225-229	208-212	205-210		
17-Norethisterone	200-207	199			
β-Estradiol	178	169			
α-Estradiol	225	223			
Estradiol benzoate	188-195	177.5	176		
Estradiol dipropionate	107	97	82		
Estradiol 17-propionate	198-200	154-156			
Estrone	260-263	256	254		
Estrone methyl ether	172-174	123-126	88-92		
Prednisolone	218-234	215			
Prednisolone acetate	232-241	225-228	217-220		
Progesterone	131	123	111	106	100
Testosterone	155	148	144	143	
Testosterone isobutyrate	131-133	88-90			
Testosterone nicotinate	194-196	185-188			
Testosterone Propionate	122	74			

[a] Data from Kuhnert-Brandstatter (1971)

.....

表5 Melting Points of Polymorphs of Barbiturates [a]

Compound	Melting point of form (℃)										
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Allobarbital	173	122									
5-Allyl-5-(2-Cyclopentenyl-1-yl)-barbituric acid	148	126	124	125							
5-Allyl-5-phenylbarbituric acid	159	133	130	129	128	126					
Amobarbital	157	151									
Aprobarbital	141	139	133	130	116	95					
Barbital	190	184	183	181	176	159					
Butalloylonal	131	128	104								
Buthalitone	149	117	95								
5-Crotyl-5-ethylbarbituric acid	117	90									
Cyclobarbital	173	161									
5,5-Dipropylbarbituric acid	148	146	126	120	110	105	85				
Dormouit	171	146									
Ethallobarbital	160	149	137	129	117	108					
5-Ethyl-5(1-piperidyl)-barbituric acid	217	210	204								
Heptabarbital	174	150	145	143	141	137	127	100			
5-Methyl-5-phenylbarbituric acid	226	226	200								
Pentobarbital	176	174	167	163	160	157	153	141	133	126	112
Propallonal	184	180	179	127	123						
Thiothyr	146	125									
Vinbarbital	166	129	106								

[a] Data from Kuhnert-Brandstatter (1971)

" (page 3, line 9 to page 8, Table).

(2b) "It is considered that crystalline state of drugs is also affected by the drug formulation process, and those changes in properties affect physical stability, chemical stability, dissolution rate, etc. of the drugs 15)" (page 11, lines 5 to 6).

(2c) "Salts and crystal forms of the active pharmaceutical ingredients greatly influence solubility, solid stability, dispersibility, and solid-liquid separation characteristics (refining efficiency). Particularly, in oral drugs, since the solubility influences bioavailability, it is a very important item for examination in research and development of drugs" (page 14, lines 6 to 1 from the bottom).

C Publication 3

(3a) "5) Polymorphism

The term is used for substances having the same chemical composition but different crystal structures.

.....

Polymorphs in drugs are often caused by selection of the type of solvent and temperature. Normally, crystals that have unstable form (metastable form) are formed initially and are transformed to a stable form under the same conditions.

... Crystal polymorphs are known for many kinds of drugs, such as prednisolone, sulfonamides, phenobarbital, and chloramphenicol palmitate, and it has been reported

that there are apparently differences in solubility and absorption between polymorphs. .....

Also, with respect to Aspirin 27), there are mp. 143~144°C (JP) Aspirin Type I obtained by recrystallization from alcohol, and mp. 123~125°C metastable form Type II obtained by recrystallization from n-hexane, and Type II is easily transformed to Type I. Compared to Type I, Type II is far more soluble to water (in this case, the dissolution rate is higher) and its concentration in blood is higher.

.....

Since operation for obtaining Type II crystals by recrystallization is quite simple, it can be deemed that reexamining aspirin, which has been called the biggest hit in the field of drug in this century, to create special formulation such as excellent aspirin suppository suggests the approach for in-house prescription in the future" (page 142, line 8 to page 145, line 3).

D Publication 4

(4a) "Polymorphism refers to a phenomenon in which substances that have common chemical composition but have a different crystal structure from each other and exhibit different crystal forms, or a substance that shows such a phenomenon. Namely, since polymorphism is caused by the difference in spatial sequence of atoms or molecules in crystals, it cannot be discriminated if the crystals are melted or dissolved.

As substances that exhibit polymorphs ... there are cortisone acetate, progesterone, prednisolone, barbital, phenobarbital, etc. as drugs and, recently, existence of polymorphism has been confirmed in many drugs.

Since polymorphs have different atom or molecular sequences in the crystal, the existence of polymorphs can be checked by the X-ray diffraction method, the density measuring method, polarization microscopy, or infrared spectrophotometry. Meanwhile, from a thermodynamic point of view, polymorphs are understood to be different habits, and each polymorph has a respective melting point and solubility. In any drug that has polymorphs, the crystal with higher melting point is the stabilized form and has lower solubility. The metastable form has lower melting point and higher solubility compared to the stable form, but, in reality, stable crystals tend to be formed during measurement, and, in such a case, solubility is determined by the stable crystal and solubility of the metastable crystal cannot be obtained.

.....

In pharmaceutical preparations, problems caused by polymorphism are due to difference in dissolution rate. As seen in the example of steroids, there is a significant

difference between stable and metastable forms. Stable form chloramphenicol palmitate is very slightly soluble, and it cannot be used as a material for formulation" (page 102, line 6 from the bottom to page 103, line 22).

(4b) "Even if drugs are the same, if there is any difference in stability of crystalline state, the unstable one has high solubility to water, and the dissolution rate is also high. Influences of polymorphism and crystalline water are known as factors that influence the absorption rate of the drug. Existence of polymorphism is known for steroids, sulfonamides, barbiturate, and antibiotics. ...

In general, with respect to crystalline water, crystals with crystalline water are more stable than anhydrides, but the latter have higher solubility" (page 232, line 7 from the bottom to page 233, line 4).

E Publication 5

(5a) "Polymorphism: A phenomenon in which identical compounds have different crystalline structures and crystal forms. Crystals of polymorphs differ in X-ray diffraction image, melting point, refraction index, and solubility. Many compounds have polymorphs, and, crystal polymorphs have been reported with respect to many drugs, including aspirin, indomethacin, cacao butter, glyceride, fatty acid, sulfonamides, cephaloridine, barbitals, chloramphenicol palmitate, steroid hormones (such as prednisolone and estrin), and riboflavin. 3) For progesterone, five crystal forms are known.

It is pharmaceutically important that solubility differs between crystal polymorphs, and, in many cases, the solubility (or, dissolution rate) of the crystal limits absorption in the digestive tract, and the drug with higher solubility is absorbed more quickly. A polymorph that is less stable (meta-stable form) has a lower melting point than the stable form and a higher solubility. According to Ostwald, when crystals precipitate from a solution, the metastable form crystalizes first (law of successive transformation). Transformation of the crystal form occurs by solvent used for recrystallization, crystallization rate (cooling rate), storage temperature conditions, trituration, etc. For example, aspirin recrystallized from 95% ethanol and aspirin recrystallized from n-hexane have different crystal form and the latter dissolves in water far quicker than the former" (page 111, lines 3 to 18).

F Publication 6

(6a) "Precipitation and recrystallization technologies are known as the oldest means for isolation and purification of compounds. In line with the development of science,

various new methods for isolation have appeared and put into practical use, but precipitation and recrystallization still occupy a major share in isolation and purification, and their importance has not been reduced.

Precipitation is an operation in which reagent is added to a solution comprising the target substance and changes the target substance into a poorly soluble compound for isolation. Accordingly, the precipitation method is always accompanied by chemical change for changing the target substance into a poorly soluble compound. On the other hand, the crystallization method is a method in which the target substance is crystallized using mainly physical change through concentration of the target substance from a solution or other operations. Since products of chemical reaction are products of crystalline precipitation in many cases, precipitation and crystallization are used while not strictly discriminating them" (page 159, lines 5 to 14).

(6b) "the major role of solvents in isolation and purification is to dissolve the compound to be precipitated and, then, precipitate deposits (crystals) by cooling or concentration through evaporation.

.....

表 5・1 有機化合物の結晶化に用いられる普通の溶媒

溶媒	化学式	分子量	融点 [°C]	沸点 [°C]
アセトン	CH_3COCH_3	58.08	−94.3	56.3
クロロホルム[a,b]	$CHCl_3$	119.39	−63.5	61.2
メチルアルコール	CH_3OH	32.04	−96	64.65
エチルアルコール	C_2H_5OH	46.07	−114.5	78.3
水[a]	H_2O	18.02	0	100
ピリジン	C_5H_5N	79.10	−42	115.5
氷酢酸	CH_3CO_2H	60.05	16.6	118.5
エチルエーテル	$C_2H_5OC_2H_5$	74.12	−116.3	34.60
酢酸エチル	$CH_3CO_2C_2H_5$	88.11	−83.6	77.1
ペンタン	$CH_3(CH_2)_3CH_3$	72.15	−130.8	36.2
ヘキサン	$CH_3(CH_2)_4CH_3$	86.18	−94.3	68.8
四塩化炭素[a,b]	CCl_4	153.84	−22.6	76.7
ベンゼン	C_6H_6	78.11	5.49	80.13
ヘプタン	$CH_3(CH_2)_5CH_3$	100.21	−90	98.4

a: 不燃性, b: 有毒, (日本化学会編: 化学便覧による)

表 5.1 化合物の結晶化に用いられる普通の溶媒

Table 5.1 Normal solvents used for crystallization of compounds

溶媒 Solvent

化学式 Chemical formula

分子量	Molecular weight
融点	Melting point
沸点	Boiling point
アセトン	Acetone
クロロホルム[a, b]	Chloroform[a, b]
メチルアルコール	Methyl alcohol
エチルアルコール	Ethyl alcohol
水[a]	Water[a]
ピリジン	Pyridine
氷酢酸	Glacial acetic acid
エチルエーテル	Ethyl ether
酢酸エチル	Ethyl acetate
ペンタン	Pentane
ヘキサン	Hexane
四塩化炭素[a, b]	Carbon tetrachloride[a, b]
ベンゼン	Benzene
ヘプタン	Pentane
不燃性	Non-flammable
有毒	Toxic

From Handbook of Chemistry edited by Chemical Society of Japan (page 166, line 18 to page 168, Table 5.1).

G　Publication 7

Translation is shown below.

(7a) "Classification of solvents by statistical analysis of parameters of properties of solvents; suggestions for polymorph screening" (page 117, Title)

(7b) "The success rate of discovering a new polymorph by crystallization from a solution might increase if solvents having various properties are used for the first polymorph screening.　In this study, eight solvent parameters, namely hydrogen bond acceptability, hydrogen bond donating property, polarity/bi-polar nature, dipole moment, permittivity, viscosity, surface tension, and cohesive energy density (equivalent to square of the solubility parameter) of 96 solvents were collected.　Using cluster statistical analysis of those parameters, 96 solvents were divided into 15 groups. Those solvents groups would provide a guideline for wisely selecting solvents of various properties for polymorph screening" (page 117, Abstract).

(7c) "Polymorph screenings are carried out daily by crystallization from various solvents by traditional technique ... or high throughput crystallization technology. It is often observed that a specific crystal is preferentially crystalized from a specific solvent, especially when no seed crystal exists ... This phenomenon is caused by the effect of regulation of solvent-solute interaction in nucleation, crystal growth, solvent mediated polymorph transformation ... , and is believed to influence emergency of polymorphs. In addition to molecular solvent-solute interaction, macroscopic properties of the solvent, such as viscosity and surface tension, might also affect crystallization dynamics and emergence of polymorphs ... Therefore, success rate to discover new polymorphs during polymorph screening would increase if a group of solvents that has polymorphic properties is used..." (page 117, left column, line 1 to page 118, left column, line 8).

(7d) In a table entitled, "Appendix A. Solvent property parameters of 96 solvents," numerical values for eight parameters, "π," "Σα," "Σβ," "dipole moment," "permittivity," "cohesive energy density," "viscosity" and "surface tension" of 96 solvents are listed. Those 96 solvents are shown below by inserting numbers every five solvents.

1, 1, 1-Trichloroethane
1, 2-Dibromoethane
1, 1-Dichloroethane
1, 2-Dichloroethane
5
1, 4-Dioxan
1-Butanol
1-Iodobutan
1-Octanol
1-Pentanol
10
1-Propanol
2, 4-Dimethyl pyridine
2, 6-Dimethyl pyridine
2-Butanol
2-Heptanone
15
2-Hexanone (MBK)
2-Methoxyethanol
2-Methyl-1-propanol

2-Methyl-2-propanol
2-Pentanone
20
2-Propanol
3-Pentanone
4-Methyl-2-pentanone
2-Methylpridine
Acetic acid
25
Acetone
Acetonitrile
Acetophenone
Aniline
Anisole
30
Benzene
Benzonitrile
Benzyl alcohol
Bromoform
Butanone
35
Butane nitrile
Butyl ethanoate
Butylamine
Carbon bisulfide
Carbon tetrachloride
40
Chlorobenzene
Chloroform
m-Cresol
Cyclohexane
Cyclohexanone
45
Cyclopentanone
cis-Decalin
n-Decane

Dibromomethane
Dibutyl ether
50
o-Dichlorobenzene
Dichloromethane
Diethyl ether
Diethyl sulfide
Diethyl amine
55
Diiodomethane
Diisopropyl ether
Dimethyl disulfide
N,N-Dimethylacetamide
N,N-Dimethylformamide
60
Dimethylsulfoxide
n-Dodecane
Ethanol
Ethyl acetate
Ethylene glycol
65
Ethyl formate
Ethylphenyl ether
Fluorobenzene
Formic acid
Glycerin
70
n-Heptane
n-Hexane
Iodobenzene
Mesitylene
Methanol
75
Methyl benzoate
Methyl ethanoate
Methyl methanoate

N-Methyl-2-pyroridone
Methyl tert-butyl ether
80
Morpholine
Nitromethane
n-Octane
n-Pentane
Pentanoic acid
85
Propanoic acid
Propane nitrile
Propyl ethanoate
Pyridine
Tetrachloroethane
90
Tetrahydrofuran
Toluene
Trichloroethane
Triethylamine
Water
95
m-Xylene
p-Xylene
(pages 121 to 124).

H Publication 8

(8a) "Recrystallization [1] Recrystallization refers to an operation in which a crystalline substance is dissolved in a solvent and precipitated as crystals using an appropriate method. For that purpose, there are used methods to cool down high temperature saturated solution utilizing the difference in solubility by temperature, to evaporate the solvent and concentrate, or add another suitable solvent to the solvent to decrease solubility. Since coexisting impurities remain in the solution in many cases, it is often used as a method for purification" (page 504, right column, paragraph 017).

I Publication 9

(9a) "a. Recrystallization

As methods for purification of substances, distillation and recrystallization are basic operations. In recrystallization operation, saturated solution is prepared by dissolving a solute in a solvent upon heating, and if this solution is cooled down the solubility of the solute is lowered and excessive solute is precipitated (crystallized) and, on the other hand, impurities do not reach to form saturated solution and remain in the solution as they are. ... impurities can be removed by recrystallization.

(i) Purity of sample

Especially, for organic substances, the purity of the sample to be recrystallized should be confirmed initially by thin-layer chromatography. On this occasion, the relationship between the polarity of the used eluent and Rf value on the thin film is useful for selecting solvent for recrystallization, and rough polarity of impurities can be obtained. It is desirable that the purity of the substance to be refined is high, and, if the purity is too low, it is recommended to remove foreign substances to some extent by distillation, column chromatography, or decolorization with activated charcoal. Needless to say, judging from the principle of recrystallization, since whether refining is possible is relevant to the shape of the solubility curve, pure crystals can be obtained in many cases in which impurities exists in large amount.

(ii) Selection of solvents

For selecting recrystallization solvent, there is no given rule, and selection is conducted basically by trial and error. Accordingly, it is recommended to check solubility to the solvent and crystalline nature using samples of about 20 mg in test tubes. If it is a known compound, it is recommended to check recrystallization solvent and solubility with compound dictionaries 1). With respect to unknown compounds, it is recommended to refer to data of known compounds of homologues. However, since early times, there is an empirical rule that a homologue dissolves homologue well, and good selection can be made based on this. Namely, considerations are if the compound to be refined is hydrogen-bonding or not, whether the compound has any polar group or hydrophobic group, whether it is ionic or not, etc. Normally, if hydrogen-bonding nature and polarity are taken into consideration, it would be sufficient to select from the following 6 solvents.

Hexane < benzene < ethyl acetate < acetone < ethanol < water (in the order of polarity from low to high).

If any solvent with an intermediate polarity is necessary, either mix two solvents or refer to Table 4.5. On this occasion, polarity values (permittivity ε, solubility parameter δ, polarity values ET; the larger ε, δ, or ET is, the higher the polarity), the boiling point, and the melting point may be used as criteria for selection. Reactive

solvents and solvents having a high boiling point should be avoided if possible. There are many examples in which desorption or substitution occurred during recrystallization of organic substances with such solvents.

(iii) Heat dissolution

Dissolution is carried out by shaking up used conical flasks in a water bath, and in the case of any crystal that is difficult to dissolve, crystals shall be milled and heat dissolved for one hour in reflux stirring with magnetic stirrers. Dissolution by ultrasonic wave may be tried.

(iv) Crystallization

Deposition rate, size, and shape of crystals differ depending on cooling speed, solvent, concentration, etc. In some cases, crystal composition may differ. Generally speaking, substances having low melting point or large molecular weight are difficult to crystallize. If it is difficult to crystallize, ○ 1. Carry out cooling gradually (leave in hot-water bath); ○ 2. Add seed crystals; ○ 3. Rub the tube wall with a glass bar to create seeds; ○ 4. Leave in a refrigerator for several days to several months; ○ 5. Use mixed solvent to reduce solubility; ○ 6. Wait for natural evaporation. If cooled down quickly, in many cases, no crystals are formed, the sample becomes an oily substance, and refining cannot be carried out. Although it is not described in the article, it is not a rare case that crystals for X-ray structural analysis happened to be obtained from NMR sample tubes left alone.

(v) Confirmation of purity

For checking the purity of a substance, various instrumental analyses such as chromatography, various spectrum analyses, and elemental assay are the current methods, but melting point measurement is a method that can be carried out easily and should not be neglected. If the substance is not pure, the melting point becomes lower than the value in literature and unclear. It should be noted that liquid crystal state might be observed in some cases when the melting point is measured" (page 184, line 20 to page 186, last line).

(9b) "

表 4・5　溶媒の物理的性質と極性値

溶　媒	化学式	融点/°C	沸点/°C	誘電率 (ε)*1	E_T*1	溶解度パラメーター (δ)
1)　プロトン性極性溶媒						
水	H_2O	0	100	78.5	63.1	23.4
メタノール	CH_3OH	−96	64.65	32.6	55.5	14.2
エタノール	C_2H_5OH	−114.5	78.3	24.3	51.9	12.9
1-プロパノール	$1\text{-}C_3H_7OH$	−126.5	97.15	19.7	50.7	11.9
2-プロパノール	$2\text{-}C_3H_7OH$	−89.5	82.4	18.3	48.6	11.5
1-ブタノール	$1\text{-}C_4H_9OH$	−89.5	117.5	17.7	50.2	11.4
酢酸	CH_3COOH	16.6	117.8	6.19	51.9	10.1
2)　非プロトン性極性溶媒						
アセトニトリル	CH_3CN	−45.72	81.6	37.5	44.3	11.8
ジメチルスルホキシド	CH_3SOCH_3	18.45	189	48.9	45.0	13
ジメチルホルムアミド	$HCON(CH_3)_2$	−61	153.0	36.71	43.8	12.0
アセトン	CH_3COCH_3	−94.82	56.3	20.5	42.2	9.8
酢酸エチル	$CH_3COOC_2H_5$	−83.6	76.82	6.03	38.1	9.04
3)　塩基性溶媒						
ピリジン	C_5H_5N	−42	115.5	12.3	40.0	10.8
α-ピコリン	$\alpha\text{-}CH_3C_5H_4N$	−69.9	129	9.94	38.3	—
4)　ハロゲン化炭化水素						
クロロホルム	$CHCl_3$	−63.5	61.2	4.70	39.1	9.24
ジクロロメタン	CH_2Cl_2	−96.8	40	8.9	41.1	9.88
四塩化炭素	CCl_4	−22.9	76.68	2.23	32.5	8.58
5)　無極性溶媒						
ベンゼン	C_6H_6	5.49	80.13	2.27	34.5	9.15
シクロヘキサン	C_6H_{12}	6.5	80.8	2.02	—	8.2
ヘキサン	C_6H_{14}	−95.3	68.8	1.90	30.9	7.24

*1　25°C.

表４・５ 溶媒の物理的性質と極性値

Table 4.5 Physical characteristics and polarity values of solvents

溶媒　Solvent

化学式　Chemical formula

融点　Melting point

沸点　Boiling point

誘電率　Permittivity

溶解度パラメーター　Solubility parameter

プロトン性極性溶媒　Protonic polar solvent

水　Water

メタノール　Methanol

エタノール　Ethanol

１－プロパノール	1-Propanol
２－プロパノール	2-Propanol
１－ブタノール	1-Butanol
酢酸	Acetic acid
非プロトン性極性溶媒	Aprotic polar solvent
アセトニトリル	Acetonitrile
ジメチルスルホキシド	Dimethyl sulfoxide
ジメチルホルムアミド	Dimethyl formamide
アセトン	Acetone
酢酸エチル	Ethyl acetate
塩基性溶媒	Basic solvent
ピリジン	Pyridine
α－ピコリン	α - Picoline
ハロゲン化炭化水素	Halogenated hydrocarbon
クロロホルム	Chloroform
ジクロロメタン	Dichloromethane
四塩化炭素	Carbon tetrachloride
無極性溶媒	Non-polar solvent
ベンゼン	Benzene
シクロヘキサン	Cyclohexane
ヘキサン	Hexane

". (page 186)

J　Publication 10

Translation is shown below.

(10a) "Solid pharmaceuticals: Strategic Approach to Consideration for Legal Regulation" (page 945, Title)

(10b) "Interests in objects of solid pharmaceuticals partially derived from the guidelines for active pharmaceutical ingredients by Food and Drug Administration (FDA) that recommend detecting polymorph, hydrates, or amorphous of active pharmaceutical ingredients using "appropriate" analytical technique. Those guidelines indicate the importance of control of crystal forms of active pharmaceutical ingredients. The guidelines also state that the applicant bears responsibility for control of crystal forms of active pharmaceutical ingredients, and, if it affects bioavailability, verification of appropriateness of the controlling method.

Accordingly, it is obvious that new-drug application (NDA) must contain information on solid condition especially when bioavailability becomes a problem, or the applicant cannot be confident about scientific approach for collecting information and what kind of information is required. This review article aims to provide a strategic approach for eliminating the major part of such vagueness by indicating concept and idea not as a series of guidelines and rules but in the form of a flowchart. Since each individual compound has specific characteristics that require a flexible approach, this point is especially important. The research proposed here is a part of the process for application of investigational new drug (IND).

Solid pharmaceutical substances show various solid-state characteristics that cover a wide range and are unpredictable. Still, however, in many cases, to apply for basic physicochemical characteristics using appropriate analytical technique provides strategies for scientific and regulation-related determination with respect to behaviors in solid state. In the initial stage of developing drugs, by working through basic questions about behaviors in solid state, both the applicant and FDA can evaluate effect of change in characteristics in solid state of pharmaceutical substance. In this field, the resulting relationship between them in the initial stage not only makes it easier to ensure homogeneity of substances used during clinical study, but also leads to complete solution of the problems in solid state before proceeding to the clinical stage of development of drugs. Further benefits brought by those scientific studies are the establishment of meaningful standards with respect to solid state that sufficiently describe the solid form of pharmaceutical substances. Therefore, those standards expedite approval for partial modification in the supplier or chemical process" (page 945, left column, line 1 to right column, line 15).

(10c) "As already stated, it is beneficial to examine existence of polymorphs and hydrates of the active pharmaceutical ingredient. The reason is that they might be encountered in some steps of drug manufacturing process or during storage of the active pharmaceutical ingredients or formulations" (page 946, left column, line 5 from the bottom to the last line).

(10d) "A. Formation of polymorphs - Has any polymorph been discovered?

The first step of the polymorph decision tree is to crystalize the substance from many different solvents in order to try to answer the question whether any polymorph is possible. Water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane, and, if appropriate, mixtures thereof may be used as solvents to be used in the final crystallization step and formulation and processing steps," (page 946, right column, lines 19 to 28).

(10e) Figure 1 (page 946) entitled "Flowchart/polymorph decision tree" begins with "Has polymorph been discovered?" in the upper left corner and has the following descriptions on the lower left side (page 946).

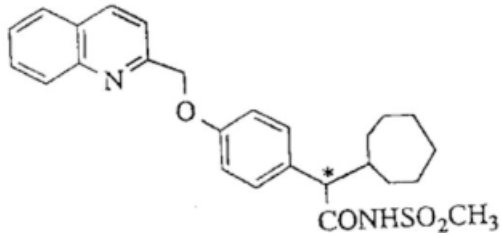
"Tests for polymorphism

- X-ray analysis of powder
- Differential scanning calorimetric analysis - Microscope
- Infrared absorption spectrum
- Solid state NMR

Means for testing are listed in Figure 6 (page 949) entitled "Flowchart for solvates or hydrates."

K Publication 11

(11a) "[Claim 1] (R)-(-)-2-cycloheptyl-N-methylsulfony-l4-(2-quinolinylmethoxy)-phenyl]-acetoamide represented by the following formula for crystalline state:

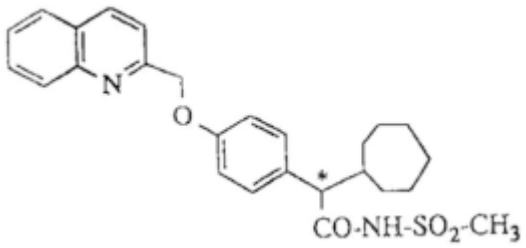


[Claim 2]

A method for manufacturing the crystalline active compound of Claim 1, characterized in that non-crystalline (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinonylmethoxy)-phenyl]-acetoamide is suspended in an inactive organic solvent, sometimes in the presence of water, and processed under increasing temperature until it is quantitatively transformed into crystalline modification, and the obtained crystals from crystalline modification are separated by a customary method and, in order to remove residual solvent that might exist, dried under a temperature 20 to 70°C until the weight decreases to a predetermined weight" (page 2, Claims 1 and 2 in the scope of claims)

(11b) "[0001] [Industrial Application Field] The present invention relates to crystal form of (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinonylmethoxy)-phenyl]-acetoamide, and a production method and use in drugs thereof.

[0002][0003][0004] [Conventional Art] (R)-(-)-2-cycroheptyl-N-methylsulfonyl-[4-(2-quinolinylmethoxy)-phenyl]-acetoamide of the following Formula (I)



that is an inhibitor of synthesis of leukotriene; a production method thereof and use in drugs thereof have been already described in EP 344,519.

[0005] According to the production method described there, the compound of Formula (I) is obtained in non-crystalline powder state. No solvate-free crystalline modification has been known so far.

[0006] However, it became clear that the amorphous compound of Formula (I) has a serious drawback in manufacturing solid drugs. Drugs comprising the amorphous compound of Formula (I) exhibit quite insufficient storage stability. This physical instability that tends to occur when preparations are stored at a temperature exceeding 30°C for a rather long period, which spoils absorption efficiency and stability of those preparations."

(11c) "[0007] [Problem to be solved by the invention] Therefore, it is very important for producing drugs to make available a compound of Formula (I) that does not have the above drawback.

[0008] [Means for solving the problem] A compound (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinonylmethoxy)-phenyl]-acetoamide in a new crystal form that has increased physical stability and reduced pressure sensitivity compared to publicly-known non-crystal form, and, therefore, is better suited to productions of various chemicals than the compound in amorphous form has been found this time."

L Publication 12

(12a) "[Claim 1] An atorvastatin hydrate of crystalline form I having X-ray powder diffraction that includes at least either one of 2θ values: 11.9 or 22.0 measured by using CuKα radioactive ray.

.....

"[Claim 9] An atorvastatin of crystalline form II having X-ray powder diffraction that includes 2θ values: 9.0 and 20.5 measured by using CuKα radioactive ray or hydrates thereof" (Claims 1 and 9 in the scope of claims).

(12b) "[0001] [Background of the invention] The present invention relates to atorvastatin in a new crystalline form that is useful as a drug and known by the chemical

name, [R-(R*, R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt, methods for manufacturing and isolating this compound, a pharmaceutical composition comprising this compound and a pharmaceutically acceptable carrier, and a pharmaceutical method for treatment. A new crystalline compound of the present invention is a useful blood hypolipidemic drug and a blood hypocholesterolemic drug.

.....

[0007] The above method of U.S. Patent discloses amorphous atorvastatin that has filtration and drying characteristics not adequate for large-scale production, and requires protection against heat, light, oxygen, and humidity."

(12c) "[0008] To our surprise, and unexpectedly, it was found that atorvastatin can be manufactured in crystalline form. Namely, the present invention provides atorvastatin in new crystalline forms called Form I, Form II, and Form IV. Compared to the conventional amorphous product, Form I atorvastatin has smaller particles and a distribution of even size, and exhibits more favorable filtering and drying characteristics. In addition, Form I atorvastatin is purer and more stable than the amorphous product."

(12d) "[0038] The present invention provides a method for manufacturing crystalline Form I atorvastatin consisting of crystallization of atorvastatin from a solution in a solvent under conditions that give crystalline Form I atorvastatin. Correct conditions under which crystalline Form I atorvastatin is formed can be determined empirically, and many methods that can be found appropriate for formation can be given.

[0039] Namely, for example, crystalline Form I atorvastatin can be produced by crystallization under controlled conditions. In particular, it can be produced, for example, by adding calcium salt such as calcium acetate, from aqueous solution of the corresponding basic salt, for example, alkali metal salt such as lithium salt, potassic salt, and sodium salt; ammonia or amine salt; preferably sodium salt, or by suspending amorphous atorvastatin in water. Generally, it is preferred to use a hydroxyl auxiliary solvent such as a lower alkanol or methanol.

[0040] If the starting substance for producing desired crystalline Form I atorvastatin is a solution of corresponding sodium salt, a preferred production method is to treat a solution of the sodium salt in water comprising about 5 v/v% or more of methanol, preferably about 5 to 33 v/v% of methanol, particularly preferably about 10 to 15 v/v% of methanol with aqueous solution of calcium acetate at a high temperature up to about 70°C, for example about 45 to 60°C, particularly preferably about 47 to 52°C. Generally, it is preferred to use 1 mol of calcium acetate to 2 mol of sodium salt of atorvastatin. Under those conditions, formation of calcium salt and crystallization

must be carried out, preferably at a high temperature, for example, within the above-mentioned temperature range. It is found that it is advantageous to include a small amount, for example, about 7 w/w%, of methyl tertiary butyl ether (MTBE) in the starting solution. It has been found that, in order to produce crystalline Form I atorvastatin consistently, it is preferable to add "seeds" of crystalline Form I atorvastatin to the solution for crystallization.

[0041] If the starting substance is amorphous atorvastatin or a combination of amorphous atorvastatin and crystalline Form I atorvastatin, desired crystalline Form I atorvastatin can be obtained by, until transformation into required form is completed, suspending the solids in water comprising up to about 40 v/v%, for example about 0 to 20 v/v%, particularly preferably about 5 to 15 v/v% of auxiliary solvent, such as methanol, ethanol, 2-propanol, acetone, etc. and filtering. It has been found that in order to ensure complete transformation to crystalline Form I atorvastatin, it is advisable to add "seeds" of crystalline Form I atorvastatin to the suspension. Instead of doing so, water-wetted cakes primarily consisting of amorphous atorvastatin, until a significant amount of crystalline Form I atorvastatin exists, can be heated to high temperature, for example, up to about 75°C, particularly preferably about 65 to 70°C, and, by doing so, mixture of amorphous/suspension Form I can be changed into slurry as mentioned above."

(12e) "[0042] Crystalline Form I atorvastatin can be isolated far more easily than amorphous atorvastatin, and, after cooled down, it can be filtered from the medium for crystallization washed and dried. For example, filtration of 50 ml of crystalline Form I atorvastatin was completed within 10 minutes. A similar amount of sample of amorphous atorvastatin required one hour or more for filtration."

(12f) "[0043] The present invention provides a method for producing crystalline suspended II atorvastatin consisting of suspending atorvastatin to a solvent under conditions to give crystalline Form II atorvastatin. Correct conditions under which crystalline Form II atorvastatin is formed can be determined empirically, and methods that can be found appropriate for formation can be given.

[0044] Namely, for example, if the starting substance is amorphous, a combination of amorphous and Form I, or crystalline Form I atorvastatin, desired Form II crystalline atorvastatin can be obtained by, until transformation into required form is completed, suspending the solids in methanol comprising about 40 to 50% water and filtering."

(12g) "[0060] [Examples] Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (Form I

atorvastatin)

Method A

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pirrol-3-carboxyamide (atorvastatin lactone) U.S. Patent No. 5,273,995) (75 kg), and methyl tertiary butyl ether (MTBRE) (308 kg), (190 L) was subjected to reaction at 48 to 58°C with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) and for 40 to 60 minutes to form ring-opened sodium salts. After cooling down to 25 to 35°C, the organic layer was disposed of, and the aqueous layer extracted with MTBE (230 kg). The organic layer was disposed of, and MTBE saturated aqueous solution of the sodium salt in MTBE was heated to 47 to 52°C. A solution of calcium acetate hemihydrate (11.94 kg) in water (410 L) was added to the solution over at least 30 minutes. Immediately after adding the solution of calcium acetate, a slurry of crystalline Form I atorvastatin (1.1 kg in water 11 L and methanol 5 L) was added to the mixture as 'seeds.' After that, the mixture was heated for at least 10 minutes to 51 to 57°C, and, then, cooled down to 15 to 40°C. The mixture was filtered and washed with a solution of water (300 L) and methanol (150 L), and then washed with water (450 L). The solid was dried under vacuum at 60 to 70 °C for 3 to 4 days and crystalline Form I atorvastatin (72.2 kg) was obtained.

Method B

Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin (1 g) were stirred in a mixture of water (170 ml) and methanol (30 ml) at about 40°C for 17 hours in total. Crystalline Form I atorvastatin (9.7 g) was obtained by filtering the mixture, rinsing with water, and drying under reduced pressure at 70°C."

(12h) "Example 2

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (Form II atorvastatin)

A mixture of amorphous atorvastatin and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 ml) and water (800 ml) and stirred for 3 days. This substance was filtered and dried under reduced pressure at 70°C, and crystalline Form II atorvastatin was obtained."

M Publication 13

Translation is shown below.

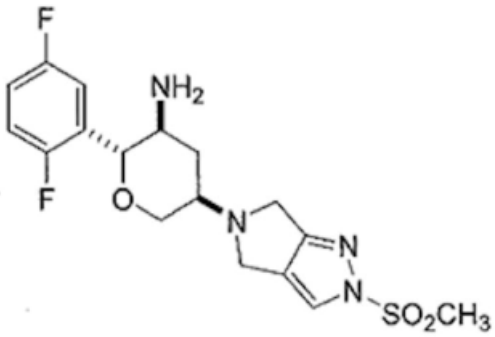
(13a) "Polymorphs in development of process" (page 527, Title)

(13b) "Crystalline products are generally easiest to isolate, refine, and dry, and, in batch process, to handle and formulate" (page 527, left column, lines 1 to 3).
(13c) "Polymorphs have a crystal lattice that has different binding method of the same molecule in a unit cell. The difference reflects difference in the way of packing molecules in the cell and change in steric configuration and can be significant. Hydrogen bonding would be relevant to almost all molecules in which the pharmaceutical industry has an interest" (page 527, left column, lines 15 to 20).
(13d) "It seems that which polymorph from possible polymorphs can be obtained depends on various factors such as the temperature at which crystallization occurs, nature of the solvent (hydrophilic, or hydrophobic), and the degree of oversaturation at which crystallization begins. Use of seed crystals is useful for obtaining targeted polymorphs" (page 527, right column, lines 9 to 14).
(13e) "Only a small number of compounds are developed, and a still smaller number of compounds are marketed. In order to give the best opportunity for progress to each candidate for development, it seems better to search for polymorphs rather than waiting for emergence of a polymorph left to chance. Techniques used in trials for obtaining polymorphs include causing crystallization under different temperatures from various solvents (polar, non-polar, hydrophilic, and hydrophobic) by cooling the solution quickly, adding a second solvent to which the solute is hard to dissolve, stirring excessive solids vigorously together with a solvent, heating excessive solids together with solvent having a high boiling point, causing to sublimate, or changing pH of a solution abruptly to cause precipitation of an acidic or basic substance" (page 528, left column, lines 2 to 14).

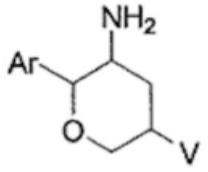
3 Invention described in Publication

Publication 1 is a patent document relating to a substituted 3-aminotetrahydropyran compound that is useful for treating Type 2 diabetes, etc., as an inhibitor of dipeptidyl peptidase IV (indicated matter (1a) to (1h)).

Publication 1 shows, with respect to above substituted 3-aminotetrahydropyran compound, in Claim 18 a specific compound



and, this is a compound that falls under the compound of Structural Formula I



(I)

(Note by the trial decision: Explanation of V and Ar is omitted) described in Claim 1.

In addition, Publication 1 discloses that the compound described in the above Claim 18, (2R, 3S, 5R)-2-(2, 5-difluorophenyl)-5-[2-(methylsulfonyl)-2, 6-dihydropyrrolo [3, 4-c] pyrazole-5 (4H)-yl] tetrahydro-2H-pyran-3-amine, was actually synthesized in Example 1 by preparing intermediates and analyzed with 1H NMR and LC-MS (indicated matter (1e) to (1g)). IC50 of dipeptidyl peptidase IV inhibition is also shown (indicated matter (1c)). In Example 1, since crude products from synthesizing reaction were refined with a column (Eluate is 1.25 to 5% MeOH and 0.125 to 0.5% ammonium hydroxide in dichloromethane) and, after that, recrystallized (60°C, recrystallization solvent is 5:1 EtOAc/CH2C12), it is acknowledged that the product of Example 1 is crystalline.

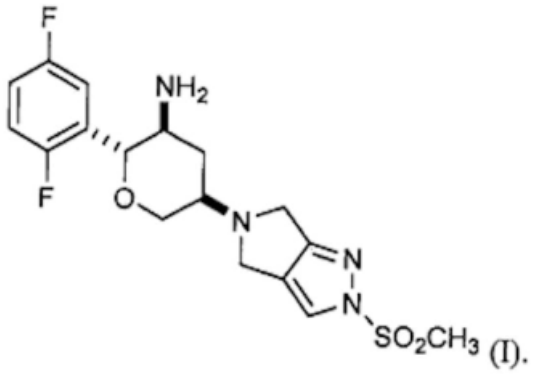
Judging from the above, it can be deemed that Publication 1 describes the invention of "a crystal of (2R,3S,5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]-5(4H)-yl]tetrahydro-2H-pyran-3-amine" (hereinafter, referred to as "Cited Invention" and the compound is referred to as "Cited Compound").

4 Comparison between the Invention and the Cited Invention

The Invention and the Cited Invention are compared.

The Cited Invention is "Compound I" of the Invention; namely, a compound the same as "(2R,3S,5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5-(4H)-yl]tetrahydro-2H-pyran-3-amine" having the following chemical structure

"



(I).

" (hereinafter, this compound is referred to as "compound P"). In addition, since "crystal of the Cited Compound" of the Cited Invention means that the Cited Invention is crystalline, it means in fact the same thing as "crystalline Cited Invention."

Then, the Invention and the Cited Invention coincide with each other in that they relate to "crystalline compound P," and differ from each other in the following point.

(Different Feature)

While, in the Invention, crystalline compound P is specified as "Form I" crystal that is characterized as "having at least four peaks selected from a group consisting of 10.3 ± 0.1 2θ, 12.7 ± 0.1 2θ, 14.6 ± 0.1 2θ, 16.1 ± 0.1 2θ, 17.8 ± 0.1 2θ, 19.2 ± 0.1 2θ, 22.2 ± 0.1 2θ, 24.1 ± 0.1 2θ and 26.9 ± 0.1 2θ in its powder X-ray diffraction pattern," Cited Invention is not specified in such a way.

5 Examination on Different Feature

A Motivation for obtaining crystals

As of the priority date of this application, generally speaking, it is acknowledged that there is a strong motivation to make substances crystallized with respect to medical compounds since crystallized substances excel in stability, purity, and easiness in handling. So, a person skilled in the art normally endeavors conditions to obtain crystallized medical compounds although there is no need to refer to the literature. It is well known that different types of crystals are sometimes obtained according to crystallization conditions. For example, with respect to crystallization, refining to improve purity of compounds is shown in indicated matters (6a), (8a), and (9a). Search for crystal polymorphs is shown in indicated matters (2a) to (2c), (3a), (4a), (4b), (5a), (10a) to (10e), and (13a) to (13e) since properties such as stability, solubility, and bioavailability vary according to a form of a medical compound crystal. The indicated matters (7a) to (7d) show that polymorph screening is ordinarily conducted and solvent property parameters are studied for selecting a solvent.

As described in 3 above, since the Cited Compound is a compound intended for pharmaceutical treatment of Type 2 diabetes, etc. as an inhibitor of dipeptidyl peptidase IV, high purity of the Cited Compound is sought in the first place to prevent unexpected side effects caused by impurities. In addition, a person skilled in the art often studies crystal polymorphs of the Compound.

Therefore, with respect to the compound P, there should be a sufficient motivation for a person skilled in the art to consider conditions to obtain crystallized compounds and analyze the crystals obtained.

B Regarding the specific process employed and the numerical value of 2θ of X-ray powder diffraction specified

(A) As for the method for obtaining the crystalline compound P with Form I disclosed in the present specification, there is a description that "Form I was produced by direct crystallization of the amorphous free base of Compound I in ethyl acetate" in paragraph [0069]. No detail of this "direct crystallization" is disclosed in the present specification, but it can be understood that it literally means a crystallization by means of ethyl acetate solution or suspension in ethyl acetate solution.

A method for crystallization based on the solution to obtain crystal polymorphs is very well known. In addition, the method to vigorously stir excessive solids with a solvent is also a method that a person skilled in the art normally adopts as described in Publication 13 (Chemistry & Industry, 21, 1989, p. 527 to 529) (a document that points out importance of study on crystals of chemical substances, especially crystal polymorphs) (indicated matter (13e)), and, in Publications 11 and 12, a method to cure suspension is adopted (indicated matters (11a), (12d), and (12f) to (12h)). On the other hand, ethyl acetate is a common solvent or a disperse medium, and it is described in Publication 6 as one out of 14 normal solvents used for crystallization of organic compounds, in Publication 9 as one out of 6 solvents initially selected for re-crystallization, and in Publication 10 as one out of 9 solvents used for searching crystal polymorphs (indicated matters (6b), (9a), (9b) and (10d)).

Therefore, the crystallized compound P with Form I should be deemed to be only a crystal obtained by trial and error that a person skilled in the art can normally exercise, for example, by substituting some re-crystallization steps during obtaining crystal of the Cited Compound P of the Cited Invention since the method disclosed in the present specification is not a technique that a person skilled in the art extraordinarily adopt and that requires extraordinary conditions.

(B) The Different Feature that specifies the numerical values of 2θ of X-ray diffraction pattern is only an indication obtained from an analysis of X-ray powder diffraction that a person skilled in the art normally conducts for the crystals obtained since X-ray powder diffraction is often conducted for an analysis of a medical compound that is expected to be crystalline (See, for example, indicated matter (10e) of Publication 10 (Pharmaceutical Research, 12(7), 1995, pp. 945 to 954), a review document for techniques for obtaining solid pharmaceuticals), .

C Accordingly, while the Invention is an invention of the crystallized compound P with Form I, the Invention is only a crystal made from the compound P disclosed by Publication 1 by applying a technique that a person skilled in the art normally adopts for crystallization when the crystallization is taken into consideration. Namely, a person skilled in the art could have easily made the Cited Invention have the property according to the Different Feature that the Invention has by dissolving and/or suspending the compound in ethyl acetate solution, examining various conditions, and analyzing the crystals obtained.

6 Regarding the effects

The present specification, paragraph [0007] recites "Certain crystalline forms, have advantages in the preparation of pharmaceutical composition of compound P, such as ease of processing and crystallization, handling, stability to stress, and dosing. In particular, they exhibit improved physicochemical properties, such as stability to stress, rendering them particularly suitable for the manufacture of various pharmaceutical dosage forms" and paragraph [0019] recites "The crystalline forms of the present invention exhibit pharmaceutical advantages over the amorphous free base of Compound I as described in WO 2010/0956708 in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In particular, the enhanced chemical and physical stability of the crystalline forms constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient." In addition, paragraph [0033] recites "The crystalline forms of Compound 1 of the present invention have been found to possess relatively high solubility in water (about 2 mg/ml), rendering them especially amenable to the preparation of formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of active pharmaceutical ingredient." However, those are not described specifying what crystal

form among Form I to Form IV disclosed in the present specification is in question.

On the other hand, the description that specifies Form I is "having Form 1 as the most stable phase above 13°C" in paragraph [0070].

However, it is as already stated in 5 above that a person skilled in the art could have easily conceived to make the Cited Invention as crystalline compound P of Form I provided with the configuration of the Invention according to the Different Feature, and it is understood that such crystal form naturally has a feature to be a crystal that is in most stable phase at a temperature above 13°C and, even if there is another feature related to pharmaceutical formulation, since it must be the same, such feature cannot be acknowledged to be especially remarkable. In addition, since it is well known that it is easier to obtain stable crystals than to obtain metastable crystals (indicated matter (3a) (4a)), it cannot be acknowledged that the stability of Form I is an especially remarkable effect that cannot be foreseen.

Judging from the above, the operational advantages of crystalline compound P of Form I of the Invention cannot be deemed to be especially remarkable.

7 Summary

Accordingly, since a person skilled in the art could have easily invented the Invention based on the invention disclosed in the Publication and common technical knowledge, the appellant should not be granted a patent for the Invention in accordance with the provisions of Article 29(2) of the Patent Act.

No. 6 Closing

As described above, since the appellant should not be granted a patent for the Invention, the application should be rejected.

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

June 29, 2017

Chief administrative judge: INOUE Masahiro
Administrative judge: NAKATA Toshiko
Administrative judge: EMOTO Kayoko