Judgment rendered on April 13, 2018
2016 (Gyo-Ke) 10182 The case of seeking rescission of JPO decision (Hereinafter referred to as "First case.")
2016 (Gyo-Ke) 10184 The case of seeking rescission of JPO decision (Hereinafter referred to as "Second case.")
Date of conclusion of Oral argument: February 2, 2018

Judgment

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Main text

1. All the Claims from Plaintiffs shall be dismissed.
2. The court costs shall be borne by Plaintiffs.

Facts and reasons

No. 1 Claims

1 First case

A trial decision for Invalidation Trial No. 2015-800095 that JPO made on July 5, 2016 shall be rescinded.

2 Second case

The same as in the above item 1.

No. 2 Outline of the case

This case is a suit against a trial decision that dismissed a request for an invalidation trial. The issues are the presence or absence of: the legal interest for litigation; inventive step; and the noncompliance of the support requirement.

1 Outline of procedures at the JPO

Defendant of First case and Second case (hereinafter simply referred to as "Defendant") filed a patent application with a filing date of May 28, 1992 (hereinafter referred to as "the filing date") (priority claiming on: July 1, 1991 <Hereinafter referred to as "the priority date".>) titled "PYRIMIDINE DERIVATIVES" (Japanese Patent Application No. 1992-164009) and registered the same on May 16, 1997 (Exhibit Ko 65. Patent No. 2648897. Number of claims: 12. Hereinafter this patent is referred to as "the Patent").

Plaintiff of Second case (hereinafter referred to as "Plaintiff X") made a request for an invalidation trial on March 31, 2015 with regard to Claims 1 to 5 and 7 to 12 of the Patent as of the date (Exhibit Ko 79. Invalidation Trial No. 2015-800095. Hereinafter referred to as "the trial"). Supporting Intervener for Defendant of First case and Second case (hereinafter simply referred to as "Supporting intervener") applied for intervention to assist defendant in the trial, and after the permission was granted, Plaintiff of First case applied for the intervention as a demandant in the trial and obtained permission (according to the entire import of the oral argument). Defendant requested for correction including the correction of the scope of claims by a written correction request on August 3, 2015 (Exhibit Ko 80; cancels Claims 3, 4, 7 and 8, and adds Claims 13 to 17, which resulted in the number of the claims after correction of 13. Number of claims after correction: 13.).

The Japan Patent Office made a trial decision on July 5, 2016 to the effect that "the demand for the trial was groundless," certified copies of which were sent to Plaintiffs on July 14. In addition, after the trial decision of the other trial case became final and binding (Invalidation Trial No. 2014-800022), a patent right was deemed to

be registered with the scope of claims and the description after the correction made by Defendant with a written correction request on June 30, 2014, which involved the correction of the scope of claims (hereinafter referred to as "the correction of the case"). Accordingly, no further correction has been made by the correction made by the written correction request on August 3, 2015, which has the same content as the correction of the case. Therefore, the Japan Patent Office dismissed the latter correction made by the written correction request on August 3, 2015, since the correction was not to be made for any purpose provided in the each items of Article 134-2, paragraph (1) of the Patent Act, and also dismissed the amendment made by the demandant to the object of the demand to invalidate the patents according to Claims 13 and 15 to 17 after the correction of the case for a reason that the original object of the demand is to invalidate patents according to Claims 1, 2, 5, and 9 to 12 after the correction of the case, and made a determination about Claims 1, 2, 5, and 9 to 12 and the description after the correction of the case.

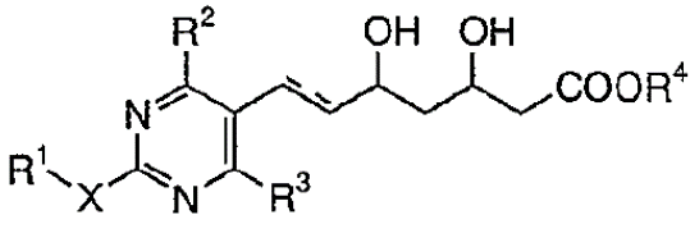
2 Recitation of the scope of claims

The recitation of the scope of claims according to Claims 1, 2, 5, and 9 to 12 of the Patent after the correction of the case is set forth as below. (The inventions of Claims 1, 2, 5, and 9 to 12 of the Patent after the correction of the case are hereinafter referred to as "the Invention 1," etc. corresponding to the claim number, and the Inventions 1, 2, 5, and 9 to 12 are collectively referred to as "the Invention," Hereinafter the descriptionattached to the written correction request (Exhibit Ko 81) is referred to as "the description".)

[Claim 1] (The Invention 1)

A compound represented by the following formula (I):

[Formula 1]



(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with halogen;

R^3 is a lower alkyl;

R^4 is hydrogen or a calcium ion forming a hemicalcium salt;

X is an imino group substituted with an alkylsulfonyl group;

the dashed line represents the presence or absence of a double bond.)

or a ring-closed lactone body thereof.

[Claim 2] (The Invention 2)

(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

[Claim 5] (The Invention 5)

A compound represented by the following formula (I):

[Formula 2]

(the chemical formula is omitted since it is the same as formula (I) of Claim 1.)

(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with a halogen;

R^3 is a lower alkyl;

R^4 is a calcium ion forming a hemicalcium salt;

X is an imino group substituted with a methylsulfonyl group;

the dashed line represents the presence or absence of a double bond).

[Claim 9] (The Invention 9)

A compound represented by the following formula (I):

[Formula 4]

(the chemical formula is omitted since it is the same as formula (I) of Claim 1.)

(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with a halogen;

R^3 is a lower alkyl;

R^4 is a calcium ion forming a hemicalcium salt;

X is an imino group substituted with a methylsulfonyl group;

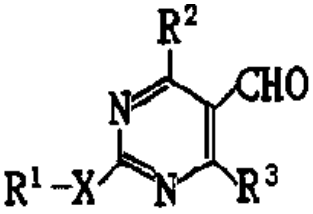
the dashed line represents the presence of a double bond.).

[Claim 10] (The Invention 10)

An optically active compound represented by the following formula (I) obtained

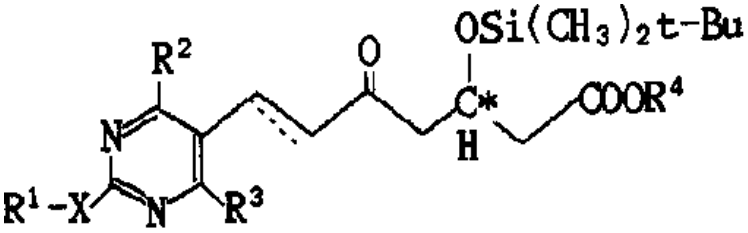
by a step of reacting a compound represented by formula (b) with a (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate derivative to produce a compound represented by formula (c);

[Formula 5]



b

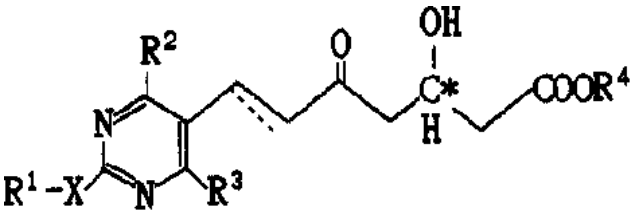
[Formula 6]



c

a step of causing tert-butyldimethylsilyl group to leave the compound represented by formula (c) so as to produce a compound represented by formula (d);

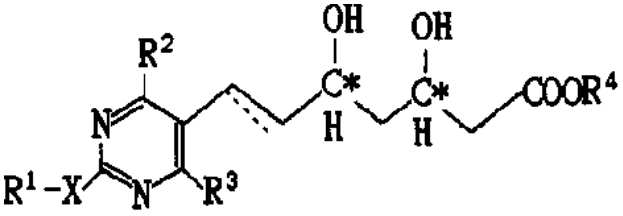
[Formula 7]



d

and a step of reducing the compound represented by formula (d):

[Formula 8]



(I)

(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with a halogen;

R^3 is a lower alkyl;

R^4 is a calcium ion forming a hemicalcium salt;

X is an imino group substituted with an alkylsulfonyl group;

the dashed line represents the presence of a double bond;
t-Bu is tert-butyl;
C* is an asymmetric carbon atom).

[Claim 11] (The Invention 11)

A calcium salt of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid.

[Claim 12] (The Invention 12)

A HMG-CoA reductase inhibitor comprising a compound of Claim 1 as an active ingredient.

3 Invalidation Reason as alleged by Plaintiffs

(1) Invalidation Reason 1 (Lack of Inventive Step with Exhibit Ko 1 with primarily cited reference)

The Inventions 1, 2, 5, and 9 to 12 were easily conceivable on the basis of the inventions described in Exhibit Ko 1 (Publication of Japanese Translation of PCT International Application No. 1991-501613) (hereinafter referred to as "Exhibit Ko 1 Invention") and Exhibit Ko 2 (Japanese Unexamined Patent Application Publication No. 1989-261377) (hereinafter referred to as "Exhibit Ko 2 Invention"; hereinafter documentary evidence with branch number includes all branch numbers, unless otherwise mentioned) and the common general technical knowledge as of the priority date, before the priority date by a person who had an ordinary knowledge in a technical field to which the invention pertains (hereinafter referred to as "a person ordinarily skilled in the art") (Article 29, paragraph (2) of the Patent Act).

(2) Invalidation reason 2 (noncompliance of support requirement)

It cannot be said that the Inventions 1, 2, 5, and 9 to 12 had significantly high activity compared to the conventional technique, and thus a person ordinarily skilled in the art could not understand that the problem to be solved by the Invention might be solved. It cannot be said that the invention for which a patent is sought recited in the scope of claims is described in the Detailed Description of the Invention (Article 36, paragraph (5), item (i) of the Patent Act prior to amendment by Act No.116 of 1994).

4 Reasons of trial decision

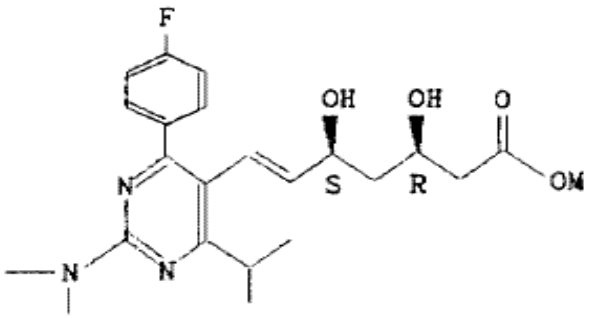
Reason of trial decision is as described in a copy of the written trial decision in the Appendix, and the gist thereof is set forth as below:

(1) Invalidation reason 1

A Invention 1

(A) Exhibit Ko 1 Invention

"

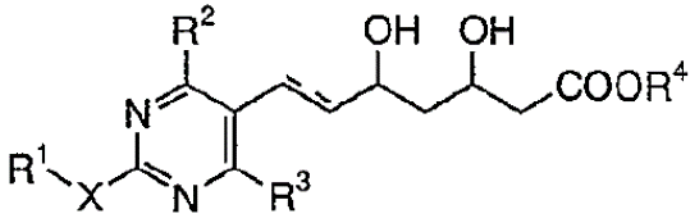


A compound (M=Na)"

(B) Common features and differences between Invention 1 and Exhibit Ko 1 Invention

[Common features]

"A compound represented by the following formula (I):



(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with a halogen;

R^3 is a lower alkyl;

the dashed line represents the presence or absence of a double bond)

or a ring-closed lactone body thereof"

[Difference]

(1-i)

In Invention 1, X is an imino group substituted with an alkylsulfonyl group, whereas in the Exhibit Ko 1 Invention it is an imino group substituted with a methyl

group.

(1-ii)

In Invention 1, R^4 is hydrogen or a calcium ion forming a hemicalcium salt, whereas in the Exhibit Ko 1 Invention it is a sodium ion forming a sodium salt.

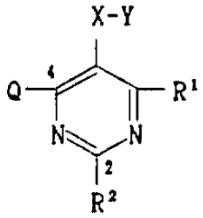
(C) Determination whether or not the difference from the cited invention can be easily conceived

a Difference (1-i)

(a) Motivation from Exhibit Ko 1 Invention

The Exhibit Ko 1 invention is one selected from

"Formula I

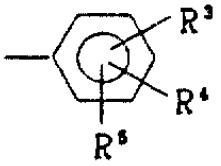


I

",

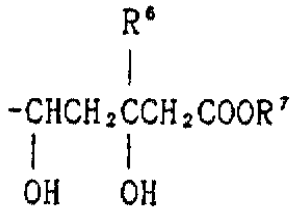
which is described in the scope of claims of Exhibit Ko 1, in which "R^1" is "isopropyl" of "C_{1-6} alkyl not including asymmetric carbon," "R^2" is "$-N(R^8)_2$," supposing that R^8 is "methyl" to be "selected independently from a C_{1-4} alkyl not including asymmetric carbon atom," and "Q" is "Q"a" of "Q""; i.e., the following structure:

"



", and any two of the "R^3," "R^4," and "R^5," are "hydrogen" and one is "fluoro," and "X" is "vinylene," and "Y" is the following structure:

"



", where "R^6" is "hydrogen" and "R^7" is a "cation" of a "sodium ion,"

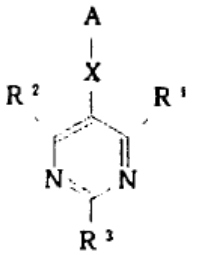
Further, the compound of the Exhibit Ko 1 Invention is obtained from Working Example 1b). Therefore, data support the pharmacological activity inhibiting "HMG-CoA reductase." On the other hand, the compound of Formula I recited in the scope of claims of Exhibit Ko 1 is prima facie described in a manner that allows us to expect such pharmacological activity, although it is not supported that the whole range of the compound of Formula I recited in the scope of claims of Exhibit Ko 1 has pharmacological activity similar to that of Exhibit Ko 1 Invention.

Further, it can be seen from the relationship between Invention 1 and formula I described in the scope of claims of Exhibit Ko 1 that Invention 1 selects "$-N(R^8)_2$" as "R^2" of the above formula I, and further selects alkylsulfonyl group ($-SO_2R'$; R' is alkyl group) for one "R^8," not "methyl" of "C_{1-4} alkyl, not including asymmetric carbon atom" as in the Exhibit Ko 1 Invention, but a compound selected from such substituent group that does not fall within the range of the above formula I.

Consequently, it cannot be said that the compound not included in formula I of Exhibit Ko 1 may be expected to have pharmacological activity inhibiting "HMG-CoA reductase activity." Therefore, it cannot be said that there is a motivation to replace "dimethylamino group" of Exhibit Ko 1 Invention with "$-N(CH_3)(SO_2R')$," which is an alternative not included into the scope of formula I.

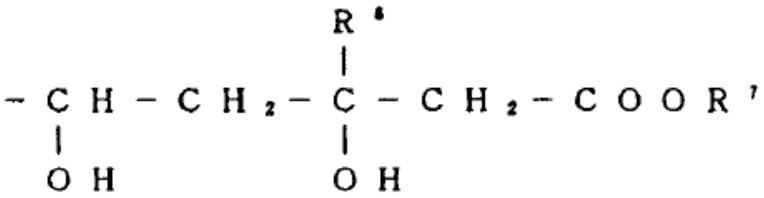
(b) Motivation from Exhibit Ko 2 Invention

Exhibit Ko 2 discloses that the "general formula"



(I)

includes: "alkyl" for "R^1," "aryl" for "R^2," "-NR^4R^5" for "R^3," "alkylsulfonyl" for "R^4," and "R^5," "-CH=CH-" for "X," "



" for "A," "hydrogen" for "R^6," and "cation" for "R^7," respectively as their alternatives. Further, it discloses that a "particularly preferable compound of general formula (I)" includes "isopropyl" for "R^1," "one monosubstituted with "phenyl" or "fluorine" for "R^2," "-NR^4R^5" for "R^3," "methyl" and "methylsulfonyl" for "R^4" and "R^5," respectively as their alternatives, and further includes "calcium cation" for "R^7" as an alternative.

The compound of general formula I of Exhibit Ko 2 also provides an HMG-CoA reductase inhibitor with a pyrimidine ring as a basic skeleton and substituents at the 2-, 4-, and 6- positions, which is in common with the Invention, like the compound of formula I of Exhibit Ko 1. The compounds included in both might partially overlap depending on a selected substituent group, but the compound of general formula (I) of Exhibit Ko 2 does not have exactly the same selectable range of substituent groups of the pyrimidine ring as the compound of the formula I of Exhibit Ko 1, but is respectively specified as a compound having a separate chemical structural formula. Given the chemical structural formula of the compound, it may become a candidate for HMG-CoA reductase inhibitor.

Further, it cannot be said that compounds with different structures may have the same HMG-CoA reductase inhibiting activity. Therefore, even if the above concept of the dimethylamino group of the Exhibit Ko 1 Invention corresponds to "-NR^4R^5" of "R^3" of the general formula of Exhibit Ko 2, there is no motivation in the first place to substitute the dimethylamino group of the Exhibit Ko 1 Invention with the substituent group not disclosed in Exhibit Ko 1 on the basis of the description of Exhibit Ko 2.

Further, each of "R^1," "R^2," and "R^3" of the compound of general formula (I) of Exhibit Ko 2 has numerous alternatives. In contrast, what is described as a specific working example where at least "X" and "A" have the same structure as in the Exhibit Ko 1 Invention is only "methylerythro-(E)-3,5-dihydroxy-7-[2,6-dimethyl-4-(4-fluorophenyl)-pyrimid-5-yl]-hept-6-enoate" of Working Example 8 (R^3 is methyl), "methylerythro-(E)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-6-methyl-pyrimid-5-yl]-hept-

6-enoate" of Working Example 15 (R^3 is phenyl), and methylerythro-(E)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-6-isopropyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate" of Working Example 23 (R^3 is phenyl). Exhibit Ko 2 fails to describe one that selects "-NR^4R^5" for "R^3". Further, regarding the compounds in which "-NR^4R^5" is substituted, Exhibit Ko 2 not does describe a production method thereof, nor pharmacological tests of HMG-CoA reductase inhibiting activity, nor the description of selecting a specific combination of "methyl" and "methylsulfonyl" for "R^4" and "R^5" in "-NR^4R^5."

Consequently, it cannot be said first of all that the specification technically supports the compound in which "methyl" and "methylsulfonyl (SO_2CH_3)" are selected for "R^4" and "R^5" just in a possible substituent group of "-NR^4R^5" that could be selected from numerous alternatives for "R^3" of the general formula (I) described in Exhibit Ko 2. It cannot be deduced from this description that there is a motivation to replace "dimethylamino group" of the Exhibit Ko 1 Invention with "-$N(CH_3)(SO_2CH_3)$."

(c) Motivation on the basis of the common general technical knowledge

It can be seen from the description of Exhibit Ko 7, Ko 10, and Ko 11 that most cholesterols are synthesized in the liver, and HMG-CoA reductase inhibitor inhibits the biosynthesis of these cholesterols. Therefore, it can be said that as of the priority date a person ordinarily skilled in the art could have recognized the technical problem to obtain a HMG-CoA reductase inhibitor with high selectivity by the liver in view of the side effects.

Subsequently, it can be deduced from the description of Exhibit Ko 7 and Ko 20 that a hydrophilic compound in HMG-CoA reductase inhibitor may possibly improve liver selectivity, although there is an exception. Thus a person ordinarily skilled in the art could recognize prima facie a motivation as of the priority date to assess the compound showing HMG-CoA reductase inhibiting activity with an indicator of hydrophilicity and select a compound with high hydrophilicity (logP of 2 or less) in order to obtain a HMG-CoA reductase inhibitor with high selectivity in the liver.

On the other hand, although both Exhibit Ko 7 and Ko 20 assessed hydrophilicity of a compound having HMG-CoA reductase inhibiting activity, they are completely silent about chemical structure to make a compound showing HMG-CoA reductase inhibiting activity hydrophilic.

Exhibit Ko 9 discloses that logP value of a target compound may be

theoretically calculated as well as πx value corresponding to a specific substituent group, which allows us to predict relative lipophilicity of a compound to be synthesized. The πx value in the case of X being "3-SO_2CH_3" (methylsulfonyl group) is -1.26 in an aromatic substituent with R and X being a substituent. It does not describe the means for modifying a compound to convert methyl group into methylsulfonyl group in order to make a compound hydrophilic, but methylsulfonyl group used herein is directly substituted with an aromatic ring, which is different in structure from the Invention 1 where the pyrimidine ring is substituted with an imino group substituted with an alkylsulfonyl group (including -$N(CH_3)(SO_2CH_3)$).

Consequently, although there is a motivation to measure hydrophilicity of compounds that have already been known to have HMG-CoA reductase inhibiting activity and select from them a compound with high hydrophilicity, it cannot always be expected that replacing a specific substituent of the Exhibit Ko 1 Invention with the other substituent may maintain HMG-CoA reductase inhibiting activity. Therefore, first of all, it cannot be said that there is a motivation in the Exhibit Ko 1 Invention to replace the specific substituent group with a methylsulfonyl group to make it hydrophilic only relying on the fact that a logP value of a compound having methylsulfonyl group becomes small (becomes hydrophilic).

Further, it is a common practice in the development of pharmaceutical compounds to change little by little the structure of a compound having a specific pharmacological activity and investigate the effect thereof. It is indefinite, however, as to what change in pharmacological effects takes place by the change of chemical structure. Therefore, it is natural to obtain a compound that may become hydrophilic within a range where at least HMG-CoA reductase inhibiting activity is maintained if one tries to obtain a compound that may become a hydrophilic HMG-CoA reductase inhibitor by modifying a chemical structure of the Exhibit Ko 1 Invention.

Exhibit Ko 16 is an article that describes synthesis of lactone of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoate and investigation of the structure-activity relationship with regard to the inhibiting activity against HMG-CoA. It discloses that the substitution at the 2-, 4- and 6- positions of the central aromatic ring (pyrimidine ring) may cause a strong biological activity in the following structural formula (omitted), and that the introduction of an isopropyl group at the 6-position (R^1) may maximize the biological activity, and that the polar substituent group at the 4-position (R^2) of 4-chlorophenyl and 4-fluorophenyl may become a strong inhibitor, and that the substitution at the 2-position (R^3) is the most important for the optimal biological activity, and the introduction of not only a bulky alkyl group but also a

phenyl moiety may achieve a significant increase of titer.

Consequently, a person ordinarily skilled in the art who read the description of Exhibit Ko 16 could not have a motivation to replace "dimethylamino group" of the Exhibit Ko 1 Invention with "-N(CH_3)(SO_2R')", which is not at all disclosed in Exhibit Ko 1 and Ko 16, while there is motivation to replace it with an alkyl group or phenyl group in view of the fact that the compound substituted with isopropyl group at the 6-position and 4-fluorophenyl at the 4-position of the pyrimidine ring, which is similar to the case of the Exhibit Ko 1 Invention, has high inhibiting activity when the substituent group at the 2-position is a bulky alkyl group or phenyl group, in combination with the fact that "C_1-C_6 alkyl not including an asymmetric carbon atom" may be selected for "R^2" of formula I of Exhibit Ko 1. Further, it cannot be said that a person ordinarily skilled in the art could conceive of selecting "-N(CH_3)(SO_2CH_3)" from them on the basis of the description of Exhibit Ko 2 that is irrelevant to Exhibit Ko 1 or Exhibit Ko 16. Further, Exhibit Ko 16 discloses that a bulky lipophilic substituent group at the 2-position of the central aromatic ring (pyrimidine ring) contributes to the biological activity of synthesized HMG-CoA reductase inhibitor. Therefore, it cannot be recognized first of all that there is any suggestion of a substituent group or substitution moiety for making the Exhibit Ko 1 Invention lipophilic.

Exhibit Ko 29 describes a search result of a compound with a substituent group of a methylsulfonyl group, which was present before the priority date. Exhibit Ko 30 also describes a compound with a substituent group of a methylsulfonyl group. It is even indefinite as to whether they are HMG-CoA reductase inhibitors. Further, it is silent about how the substituent group of the methylsulfonyl group changes the properties of the compound. Therefore, even if a compound having a substituent group of a methylsulfonyl group was present before the priority date, a person ordinarily skilled in the art could not easily conceive of modifying the dimethylamino group of the Exhibit Ko 1 Invention so as to replace the methyl group thereof with a methylsulfonyl group.

Further, referring to the other evidences distributed before the priority date, there is no description of the technical significance to replace a methyl group with a methylsulfonyl group. There is no description to motivate a person ordinarily skilled in the art to replace "dimethylamino group" at the 2-position of the Exhibit Ko 1 Invention with "-N(CH_3)(SO_2R')" for making a compound of the Exhibit Ko 1 Invention hydrophilic.

Consequently, even if a person ordinarily skilled in the art could conceive of modifying a chemical structure of the Exhibit Ko 1 Invention to obtain a hydrophilic

compound, it cannot be said that there is a motivation to replace only one methyl group of the "dimethylamino group" present at a specific position (2-position of pyrimidine ring) with a methylsulfonyl group (alkylsulfonyl group) to make "-N(CH_3)(SO_2R')" for making a compound of the Exhibit Ko 1 Invention hydrophilic.

(d) Summary

Therefore, in the Exhibit Ko 1 Invention, it cannot be said that a person ordinarily skilled in the art could easily conceive of adopting the structure of the difference (1-i). Therefore, without considering the difference (1-ii), it cannot be said that the Invention 1 was easily conceivable on the basis of the Exhibit Ko 1 Invention and the Exhibit Ko 2 Invention as well as the common general technical knowledge as of the priority date.

b The effect of the Invention 1

The effect of Invention 1 is to provide a compound that may become an effective drug showing strong HMG-CoA reductase inhibiting activity.

On the other hand, Exhibit Ko 1 discloses that the compound of the Exhibit Ko 1 Invention shows HMG-CoA reductase inhibiting activity; however, the Exhibit Ko 1 Invention fails to disclose the effect on the HMG-CoA reductase inhibiting activity if "dimethylamino group" at 2-position of pyrimidine ring is replaced with "-N(CH_3)(SO_2CH_3)," which is not included into the range of formula I. Exhibit Ko 1 discloses a compound where the 2-position of pyrimidine ring is substituted with a "4-morpholinyl group." This is just a compound where "-N(R^8)$_2$" is selected for "R^2" of formula I of Exhibit Ko 1 and further "both R^8, together with a nitrogen atom, form part of a 5-,6- or 7-membered optionally substituted ring optionally containing one or more further heteroatoms (ring B)" in the definition is selected for "R^8." It fails to disclose the effect on the activity if "-N(CH_3)(SO_2CH_3)", which does not fall within the range of formula I, is selected for "R^2."

Subsequently, Exhibit Ko 2 describes "-NR^4R^5" is selected for "R^3" of formula I, and describes both methyl and methylsulfonyl for "R^4" and "R^5" as alternatives, but it lacks any description suggesting that a methyl group and a methylsulfonyl group are equivalent substituent groups in pharmacological activity, and does not even provide any working example of a compound where "-NR^4R^5" was selected for "R^3." Thus the pharmacological activity of such compound cannot be expected from the description of Exhibit Ko 2.

Furthermore, similar to the compound of Invention 1, Exhibit Ko 16 describes a

compound with an isopropyl group at the 6-position and a 4-fluorophenyl group at the 4-position of a pyrimidine ring. The substitution at the 2-position is an alkyl group or a phenyl group. The group "-N(CH_3)(SO_2CH_3)" is not described. Therefore, it cannot be said that any compound with an isopropyl group at the 6-position and a 4-fluorophenyl group at the 4-position of a pyrimidine ring may achieve a similar level of activity without relation to the substituent group at the 2-position.

Further, pharmacological activity is closely related to the structure of a compound. If a substituent group of a compound with pharmacological activity is changed, the pharmacological activity might be lost in some cases. Therefore, it cannot be seen from not only Exhibit Ko 1, Ko 2, and Ko 16 but also the other evidences that a person ordinarily skilled in the art could have expected the effect on HMG-CoA reductase inhibiting activity of replacing a "dimethylamino group" at the 2-position of the pyrimidine ring of the Exhibit Ko 1 Invention with "-N(CH_3)(SO_2CH_3)" in a compound.

The pharmacological activity of the HMG-CoA reductase inhibiting activity of the Invention 1 being higher than that of Mevinolin sodium salt can be inferred from the description of the specification, and Exhibit Ko 3 also supports this. Therefore, the effect of the Invention 1 may not be negated.

c Summary

Therefore, it cannot be said that Invention 1 was easily conceivable by a person ordinarily skilled in the art before the filing (priority date) on the basis of the Exhibit Ko 1 Invention (main cited invention) and the Exhibit Ko 2 Invention distributed before the filing (priority date) as well as a common general technical knowledge as of the priority date.

B The Inventions 2, 5, and 9 to 12

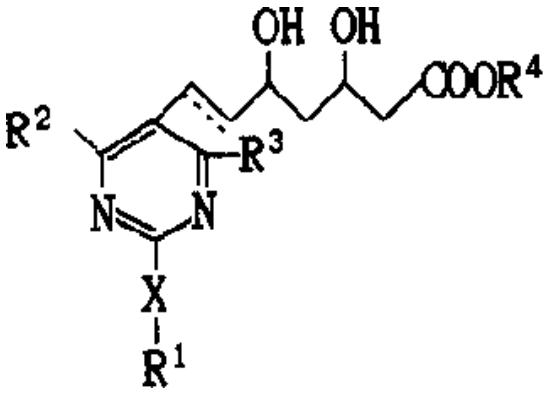
Similarly, it cannot be said that the Inventions 2, 5, and 9 to 12 were also easily conceivable by a person ordinarily skilled in the art on the basis of the Exhibit Ko 1 Invention and the Exhibit Ko 2 Invention as well as the common general technical knowledge as of the priority date.

(2) Invalidation reason 2

A Problem to be solved by the Invention

The compound represented by the following general formula (I)

"



(wherein R^1 is a lower alkyl, aryl, or an aralkyl, each of which may have one or more substituents; each of R^2 and R^3 is independently hydrogen, a lower alkyl, or an aryl, and each of said lower alkyl and aryl may have one or more substituents; R^4 is hydrogen, a lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or a sulfonyl group, or an imino group which may have a substituent; the dashed line represents the presence or absence of a double bond)"

includes the compounds of the Inventions 1, 2, 5, and 9 to 11, and the Invention 12 is directed to an HMG-CoA reductase inhibitor including the compound of the Invention 1 as an active ingredient. Therefore, the problem to be solved by the Inventions 1, 2, 5, and 9 to 11 lies in the provision of a compound having excellent HMG-CoA reductase inhibiting activity, and the problem to be solved by the Invention 12 lies in the provision of an HMG-CoA reductase inhibitor including such a compound.

Further, the Detailed Description of the Invention discloses that the Invention is directed to a "3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitor," and for such HMG-CoA reductase inhibitor there were developed synthesized HMG-CoA reductase inhibitors such as Fluvastatin and BMY22089 other than Mevinolin, Pravastatin, and Simvastatin that are obtained from fungal metabolites or their partially-modified compounds, but it fails to disclose that there is any problem for these HMG-CoA reductase inhibitors that have already been developed. Therefore, the Invention does not require more excellent HMG-CoA reductase inhibiting activity compared to the existing HMG-CoA reductase inhibitors including Mevinolin, Pravastatin, Simvastatin, Fluvastatin etc. It is recognized that a problem to be solved is to provide an HMG-CoA reductase inhibitor including a compound having "excellent HMG-CoA reductase inhibiting activity" or the compound as an active ingredient to the extent that it may become a pharmaceutical product for "suppressing the production of cholesterols."

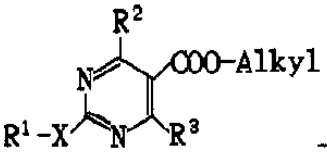
B Decision

(A) Manufacture

The Detailed Description of the Invention describes in Working Examples 1 and 2 a specific production method of "calcium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid," which is encompassed into Invention 1, the method comprising the steps of: producing "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid sodium salt" from the starting raw material (III-3); and changing from it to "(hemi)calcium salt" thereof. Further, a specific production method of the starting raw material of the compound (III-3) is also described in the reference examples 1 to 4.

The "calcium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" specifically described in the working examples corresponds to the case of formula (I) of the Invention 1 where R^1 is methyl, R^2 is phenyl substituted with fluorine, R^3 is isopropyl, R^4 is a calcium ion, X is an imino group substituted with a methylsulfonyl group, and the double bond exists. The Detailed Description of the Invention has a general description of a production method of formula (I) as well as a production method when R^4 is H in Invention 1. Further, it also discloses that the following compound a:

"



a "

is a starting material thereof. This corresponds to the above compound (III-3). A person ordinarily skilled in the art can recognize from the production examples of reference examples 1 to 4 that a partial change of the agents described therein allows for the production of compounds of formula (I) where R^1 may be not only methyl but also another lower alkyl, R^2 may be phenyl substituted with not only fluorine but also another halogen, R^3 may be not only isopropyl but also another lower alkyl, and X may be an imino group substituted with not only methylsulfonyl group but also another alkylsulfonyl group.

Consequently, it can be said that a person ordinarily skilled in the art could understand from the Detailed Description of the Invention that the compound of

Invention 1 can be actually produced; i.e., can be provided.

Inventions 2, 5, and 9 relate to a compound that confines the scope of the formula (I) of Invention 1, and the compound may be produced in a range of the formula (I) of Invention 1. Therefore, a person ordinarily skilled in the art can understand that the compounds of Inventions 2, 5, and 9 may also be produced.

Invention 10 is produced by a specific production method. The general production method as well as a specific working example are described in the Detailed Description of the Invention. Therefore, a person ordinarily skilled in the art could recognize that the compound of Invention 10 may also be produced.

Invention 11 was actually produced in the above Working Examples 1 and 2.

Therefore, the Detailed Description of the Invention is described to the extent that allows a person ordinarily skilled in the art to produce the compounds of Claims 1, 2, 5, and 9 to 11.

(B) HMG-CoA reductase inhibiting activity

The Detailed Description of the Invention discloses a measurement method of HMG-CoA reductase inhibiting activity, mixing a test compound with a mixture of a rat liver microsome solution and a solution of [3-^{14}C]HMG-CoA solution, and subsequent to incubation, applying to thin-layer chromatography plate, and scraping a part with an Rf value of 0.45 to 0.60, and measuring the specific radio-activity thereof to measure a relative activity thereof, with the relative activity of sodium Mevinolin given as 100. Further, as a result of the measurement, it discloses that compound (Ia-1) of "sodium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate" has a relative HMG-CoA reductase inhibiting activity of 442, with the inhibiting activity of sodium Mevinolin given as 100.

Compound (Ia-1) described in the Detailed Description of the Invention is a sodium salt, which is not included into Invention 1 of free acid or hemicalcium salt, but it is construed as performing a similar drug efficacy in view of the pharmacological action mechanism without relation to the form of salt. Therefore, it can be deduced that Invention 1 shows a similar HMG-CoA reductase inhibiting activity as in the case of sodium salt. In fact, according to Exhibit Ko 3, a hemicalcium salt of "S-4522" also shows a stronger HMG-CoA reductase inhibiting activity than sodium Mevinolin, which thus supports the above deduction.

Further, Invention 1 includes in its range a compound of formula (I) where R^1 is a lower alkyl, R^2 is a phenyl substituted with a halogen, R^3 is a lower alkyl, and X is an

imino group substituted with an alkylsulfonyl group. These substituent groups are very similar to those of the compound in the working examples where R^1 is methyl, R^2 is a phenyl substituted with fluorine, R^3 is isopropyl, and X is an imino group substituted with a methylsulfonyl group. The compound (Ia-1) has a higher level of activity compared to a pharmaceutical product of sodium Mevinolin. Therefore, a person ordinarily skilled in the art can recognize that Invention 1 with a very similar chemical structure will also become a compound showing a similar HMG-CoA reductase inhibiting activity, and will have an "excellent HMG-CoA reductase inhibiting activity" to the extent that it may become a pharmaceutical product "suppressing the production of cholesterols."

Consequently, it can be said that the Detailed Description of the Invention discloses to the extent that allows a person ordinarily skilled in the art to recognize that Invention 1 can solve the problem.

Inventions 2, 5, and 9 to 11 are included within the scope of Invention 1. Therefore, similarly, it can be said that the Detailed Description of the Invention discloses to the extent that allows a person ordinarily skilled in the art to recognize that these Inventions can solve the problem.

Invention 12 is an HMG-CoA reductase inhibitor including Invention 1 as an active ingredient. Therefore, similarly, it can be said that the Detailed Description of the Invention discloses to the extent that allows a person ordinarily skilled in the art to recognize that the Invention can solve the problem.

C Summary

As seen above, it cannot be said that the inventions for which a patent is sought recited in Inventions 1, 2, 5, and 9 to 12 are not described in the Detailed Description of the Invention. Therefore, it cannot be said that the recitation of the scope of claims of the specification does not comply with Article 36, paragraph (5), item (i) of the Patent Act before the revision in Heisei 6.

No. 3 Defendant's Defense against the Complaint prior to the pleading on the merits

1 Tokyo High Court judgment on December 26, 1990 (1990 (Gyo-Ke) 77, a collection of civil and administrative court decisions relating to intangible property rights, Vol. 22, No. 3, page 864) rules that "The case requests for rescission of trial decision to the effect that the request for an invalidation trial of the Patent made by Plaintiff should be dismissed. Therefore, Plaintiff obviously has a standing under the provision of Article 178, paragraph (2) of the Patent Act. It cannot be seen from the

facts that Plaintiff has a legal interest for litigation with regard to the case. Specifically, the trial decision to the effect that the request for an invalidation trial according to the demand of Plaintiff should be dismissed is formally an administrative measure against Plaintiff's interest; however, a legal interest for litigation as a requirement for a suit against trial decision made by the JPO is not satisfied by the existence of such a formal disadvantage, but required for a substantial legal interest to be recovered by the rescission of the trial decision in such circumstances where Plaintiff suffers a substantial legal disadvantage, or faces a risk of so suffering as a result of, as a legal effect, from the establishment of the JPO decision. Therefore, even if one has a legal interest for litigation to sue for the rescission of trial decision that dismissed a demand for trial to invalidate a patent during the life of the patent since he might face a risk of suffering disadvantage from the patent protection of the invention that should have been invalidated, he does not have a legal interest for litigation to sue for the rescission of trial decision that dismissed a request for an invalidation trial of the patent when the life of the patent is lapsed without causing any dispute that poses a problem as to whether the patent is valid or invalid, without any factual relationship that might possibly become a cause for escalating into such dispute in the future, and without any legal disadvantage due to the existence of the patent right being realistically or potentially substantiated."

2 The patent right has been expired due to the lapse of May 28, 2017 (Exhibit Otsu 76).

Plaintiffs did not implement any act corresponding to the acts of work of the patent right, and thus Defendant obviously has no right to demand compensation for damage, nor does Defendant have a right for litigation, etc. Therefore, a legal interest for litigation of Plaintiffs has already diminished, and thus the litigation should be dismissed.

3(1) Plaintiffs had suffered the effect of prohibitive right during the valid period of patent right, which legal disadvantage may not be recovered by the rescission of the trial decision.

Suit Against Trial Decision made by the JPO is a kind of administrative case litigation. Under the Administrative Case Litigation Act, if there is no legal interest to cancel an official action due to lapse of period, no legal interest for litigation is present. This is the precedent and the commonly accepted theory.

(2) Article 123, paragraph (3) of the Patent Act only confirms that the termination of patent right does not result in the immediate loss of legal interest for litigation. The article does not specify the ability to conduct invalidation trial or suit against trial decision made by the JPO even in the absence of legal interest for litigation.

No. 4 Argument by Plaintiffs against the defense prior to the pleading on the merits

One can request for invalidation trial even if the life of a patent is expired, which is obvious from the Patent Act. If there is any dispute between competing pharmaceutical companies on the validity of the patent for an invention regarding drug like the present case, things are different from the case of Tokyo High Court judgment on December 26, 1990 where a consultant, having almost no realistic and specific possibility for himself to be able to work an invention during a life of a patent, contended against the validity of the patent.

Plaintiffs did not conduct any act that might be seen as an infringing act of the patent right during the life of the patent right. In this sense, it is true that Defendant has no legal rights to pursue a variety of liabilities that premise the infringement of the patent right such as a right to demand compensation for damage and a right for litigation. However, it is the case where Plaintiffs had realistically and substantially suffered the effect of the prohibitive right of the Patent, and furthermore data influencing the establishment of the Patent is also doubtful. Therefore, it is natural to seek a judicial ruling in a suit against trial decision made by the JPO with regard to the validity of the Patent.

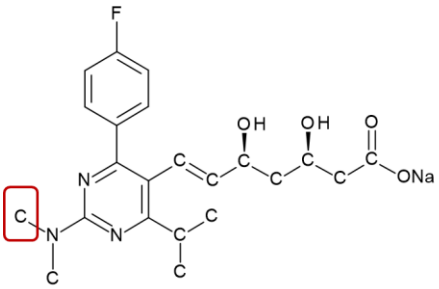
No. 5 Grounds for rescission of the JPO decision presented by Plaintiffs

1 Ground 1 for rescission (Errors in the determination of inventive step)

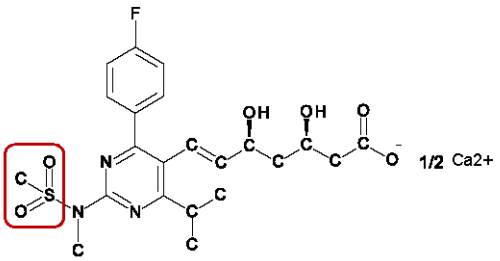
(1) Error in the determination of lack of motivation

A Motivation from Exhibit Ko 1

(A) The compound of the Exhibit Ko-1 Invention (the compound of Working Example 1b) of Exhibit Ko 1) and the structure of the compound of the Invention are shown in the following figures. The only difference (red circle part) is whether a substituent group of N atom at the 2-position of a pyrimidine ring is a methyl group or a methylsulfonyl group (Indeed there is also a difference between a sodium salt and a calcium salt, but this difference does not at all contribute to the inventive step of the compound of the Invention.).



Compound of
Exhibit Ko 1 Invention



Compound of the Invention
(Rosuvastatin)

(B) The compound of the Exhibit Ko 1 Invention has excellent in vivo activity of about 125 times higher than that of Compactin whose utility was found in human subjects, and about 15 times higher than that of Mevinolin (Lovastatin) that had been sold as a drug for lowering cholesterols as of the priority date (Test B, described in Exhibit Ko 1, page 11, right bottom column, line 21 to page 12, left upper column, line 6 (in vivo animal experiment test)).

Therefore, there was a motivation for a person ordinarily skilled in the art to make a compound of the Exhibit Ko 1 Invention a lead compound.

(C) There was an attempt as of the priority date to obtain an HMG-CoA reductase inhibitor with high liver selectivity, in view of side effects. Thus, there was a motivation for a person ordinarily skilled in the art to introduce a hydrophilic substituent group for selectively transferring a compound to the liver, the target organ of an HMG-CoA reductase inhibitor, by increasing hydrophilicity of the compound of the Exhibit Ko 1 Invention, which was a lead compound.

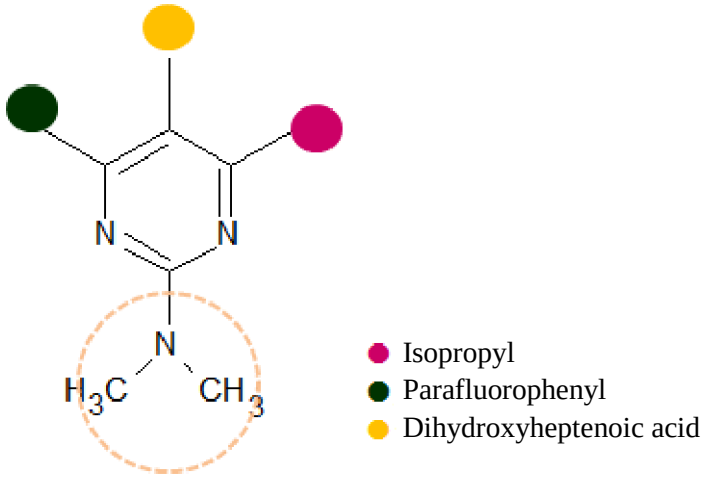
Further, in view of the common general technical knowledge as of the priority date, the introduction at 2-position of pyrimidine ring was essential to introduce a hydrophilic substituent group into the compound of the Exhibit Ko 1 Invention, and there was a motivation for a person ordinarily skilled in the art to introduce a hydrophilic substituent group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention.

In other words, the compound of the Exhibit Ko 1 Invention is shown as below, dihydroxyheptenoic acid at the 5-position of the pyrimidine ring is a so-called pharmacophore essential for activity (Exhibit Ko 15). Therefore, a person ordinarily skilled in the art would not conceive of the change of this part.

Further, in view of the fact that the combination of a p-fluorophenyl group at

the 4-position of the pyrimidine ring and an isopropyl group at the 6-position resulted in a strong activity (Comparison between Compounds 2t to 2w and 2r to 2s of "Table I" of Exhibit Ko 16, Exhibit Ko 26, Ko 27, Ko 76) and many of compounds developed at that time had this combination (Exhibit Ko 8), a person ordinarily skilled in the art would not conceive of the change of the 4-position and 6-position of the pyrimidine ring.

Therefore, a person ordinarily skilled in the art would be motivated to introduce a hydrophilic substituent group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention.



(Dimethylamino group surrounded by a dashed line binds to 2-position of pyrimidine ring. Parafluorophenyl group binds to 4-position of pyrimidine ring. Dihydroxyheptenoic acid binds to 5-position of pyrimidine ring. Isopropyl group binds to 6-position of pyrimidine ring.)

(D)a In modifying a lead compound, a principle is to modify it little by little, while maintaining a chemical structure of a lead compound as much as possible (Exhibit Ko 56 to Ko 58). Therefore, a person ordinarily skilled in the art who conceived of introducing a hydrophilic substituent group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention would substitute only one methyl group (CH_3) of the dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a hydrophilic group so that a structural change caused by the modification might be as small as possible.

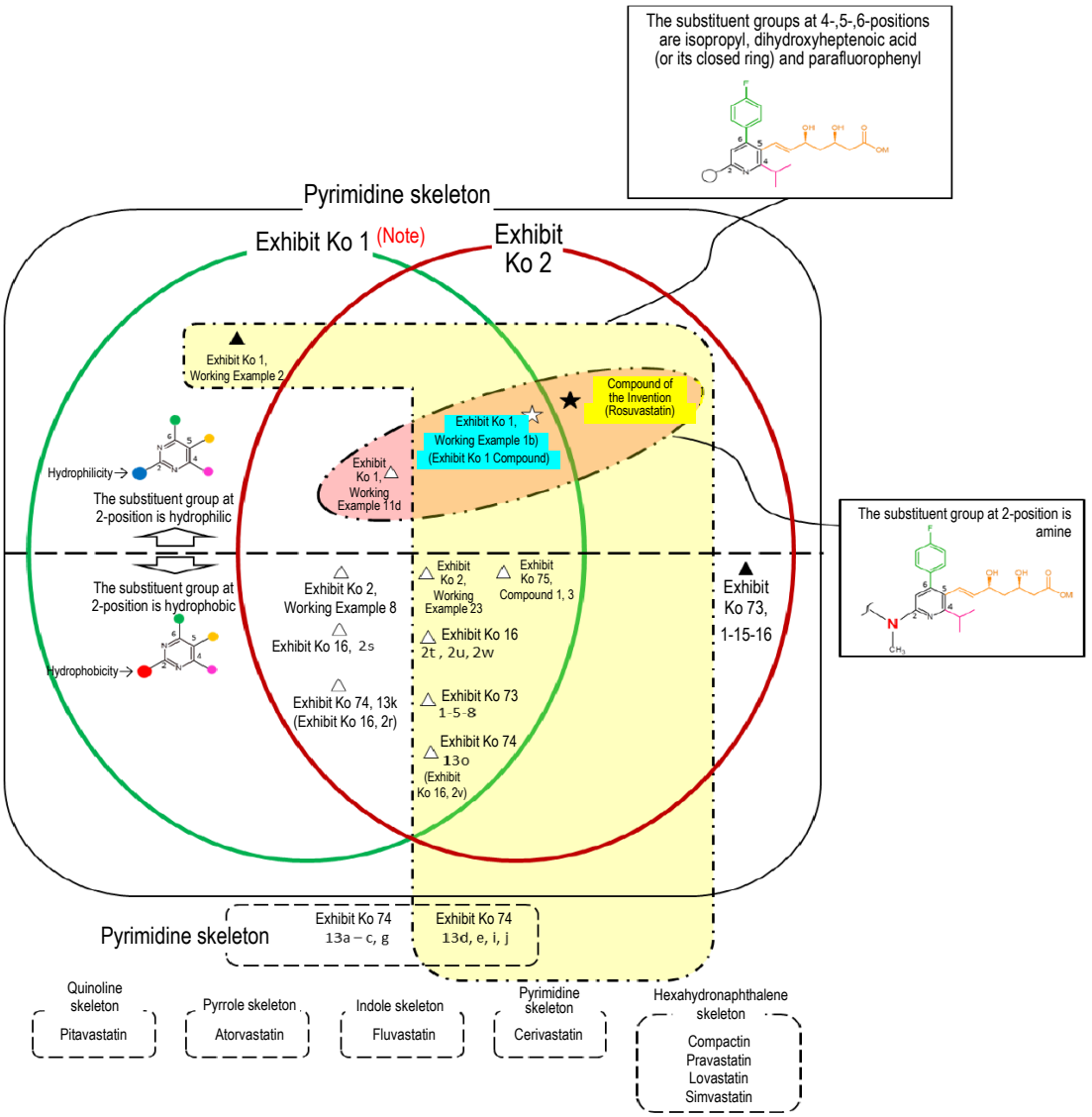
b It is publicly known that a methylsulfonyl group is the substituent group that

contributes to hydrophilicity the most (e.g. Exhibit Ko 9, Ko 28, Ko 56, Ko 59, Ko 60). Therefore, it is easy to substitute one methyl group of a dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a methylsulfonyl group.

c Taking into consideration general formula (I) of Exhibit Ko 2, it is all the more easy to substitute one methyl group of a dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a methylsulfonyl group.

In other words, general formula (I) of Exhibit Ko 2 includes the compound of the Exhibit Ko 1 Invention as an HMG-CoA reductase inhibitor, and thus there is a sufficient motivation to consider Exhibit Ko 2 for modification of the compound of the Exhibit Ko 1 Invention. General formula (I) of Exhibit Ko 2 only describes six candidates (alkyl group, aryl group, aralkyl group, acyl group, alkylsulfonyl group, arylsulfonyl group) for the substituent group of the N atom of a dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention, and it is extremely easy to select from them a methylsulfonyl group, an alkylsulfonyl group having hydrophilicity, and a small change of molecule size from a methyl group.

(E)a The relationship between general formula I of Exhibit Ko 1 and general formula (I) of Exhibit Ko 2 is shown as in the following schematic drawing:



(Note) There are few compounds of working examples, for which Exhibit Ko 1 actually confirmed the activity. There are no working examples sufficient to cover the group of compounds encompassed into the broad scope of general formula (I). Therefore, it cannot be seen that the outer edge of the range of general formula (I) of Exhibit Ko 1 was defined as a boundary between the region where the activity was confirmed and the region where the activity was not confirmed by the compounds of the working examples.

The compound of the Invention is not encompassed into the scope of general formula I of Exhibit Ko 1, but the former has common features with the compound of the Exhibit Ko 1 Invention in that the former has isopropyl, dihydroxyheptenoic acid (or its closed ring), and parafluorophenyl at the 4-, 5-, 6-positions of pyrimidine ring, and has a structure expected to exhibit a strong HMG-CoA reductase inhibiting activity.

Further, both the compound of the Invention and the compound of the Exhibit Ko 1 Invention have a hydrophilic substituent group at the 2-position of the pyrimidine ring that is expected to have a high liver selectivity, and have the common substituent

group at the 2-position of an amine having at least one methyl group.

Therefore, the compound of the Invention is not included in the scope of general formula I of Exhibit Ko 1; however, it is a compound located in the vicinity of the outer edge of the scope of general formula I.

b The scope of the claims is a scope that the applicant seeks for a patent as of the filing date, which is not consistent with a scope in which pharmacological activity may be expected.

As of the priority date, the research on the HMG-CoA reductase inhibitor of so-called statin was progressed, and it was at least known that dihydroxyheptenoic acid (or a lactone thereof) at the 5-position of the pyrimidine ring of the Exhibit Ko 1 Invention was a pharmacophore necessary for activity (Exhibit Ko 15). Therefore, a person ordinarily skilled in the art would reasonably expect pharmacological activity of a compound having the pharmacophore, even if the compound were slightly out of the scope of claims.

As set forth below, it was publicly known before the priority date that the compound slightly out of the scope of the general formula I described in the scope of claims of Exhibit Ko 1 actually had a sufficiently strong HMG-CoA reductase inhibiting activity.

(a) Compound 1-5-16 described in Exhibit Ko 73, which was publicly known before the priority date, is out of the scope of general formula I of Exhibit Ko 1 in that the 2-position of the pyrimidine ring is 4-phenyl-phenyl, but 4-phenoxy-phenyl falls within the scope of the general formula I of Exhibit Ko 1. Therefore, it is a compound that does not fall within the scope of general formula I of Exhibit Ko 1, but has a very similar structure, and is slightly out of the scope of general formula I of Exhibit Ko 1.

Exhibit Ko 73 shows that the above compound has an HMG-CoA reductase inhibiting activity comparable to or higher than that of CS-514 (Pravastatin) that had been developed as a pharmaceutical product.

(b) Except that compounds 13a to 13e and 13g to 13j described in Exhibit Ko 74, which was publicly known before the priority date, are not pyrimidine but pyridine, these compounds fall within the scope of formula I of Exhibit Ko 1. Thus, these compounds have very similar structures although they do not fall within the scope of general formula I of Exhibit Ko 1, and thus are slightly out of the scope of general

formula I of Exhibit Ko 1.

Exhibit Ko 74 discloses data showing that the above compound has an HMG-CoA reductase inhibiting activity.

c It is confirmed that a number of compounds included in a region surrounded by a dashed-dotted line in the above schematic drawing have an HMG-CoA reductase inhibiting activity (e.g. Compounds 2t to 2w of Exhibit Ko 16, Compound 1-5-8 of Exhibit Ko 73, and Compound 13o of Exhibit Ko 74). It is also confirmed that the compounds of the Exhibit Ko 1 Invention included in a region surrounded by dashed-two dotted line in the above schematic drawing and the compound of Working Example 11d of Exhibit Ko 1 also have an HMG-CoA reductase inhibiting activity. Therefore, the compound of the Invention included in a region where these dotted lines overlap should be one where pharmacological activity may be reasonably expected, even if the compound is out of the scope of general formula I of Exhibit Ko 1.

d Therefore, a person ordinarily skilled in the art would have reasonably expected a pharmacological activity (HMG-CoA reductase inhibiting activity) from a compound having a pharmacophore as an HMG-CoA reductase inhibitor, but slightly out of a scope of the claims even if the compound does not fall within a scope of the claims of Exhibit Ko 1. In view of this, the determination of the trial decision is erroneous in that it found lack of motivation because a pharmacological activity of "HMG-CoA reductase inhibiting activity" might not be expected if replaced with "-$N(CH_3)(SO_2R')$," which was an alternative not included into scope of general formula I of Exhibit Ko 1.

B Motivation from Exhibit Ko 2

(A) Exhibit Ko 2 describes a method of producing the whole range of the compounds of general formula (I) and HMG-CoA reductase inhibiting activity as in the following. Therefore, it can be seen as a technical support of the compound of the general formula (I) where "NR^4R^5" was selected for "R^3." Accordingly, the finding of the trial decision to the effect that "Exhibit Ko 2 fails to describe a production method thereof or pharmacological tests of HMG-CoA reductase inhibiting activity with respect to compounds where 'NR^4R^5' was selected for 'R^3'" is erroneous.

a Exhibit Ko 2 describes a method for the synthesis of the compound of general formula (I) (page 13, left bottom column, line 8 to page 19, right bottom

column, line 1). Thus a person ordinarily skilled in the art could understand the method for the synthesis of compound where "NR^4R^5" was selected for "R^3."

b Exhibit Ko 2 discloses that the compound of general formula (I) has an activity to the extent that it may be a pharmaceutical product capable of suppressing the biosynthesis of cholesterols (page 19, right bottom column, lines 2 to 11). Thus, a person ordinarily skilled in the art could understand that the compound where "NR^4R^5" was selected for "R^3" might have an activity to the extent that it might be a pharmaceutical product capable of suppressing the biosynthesis of cholesterols.

(B) As set forth below, it can be seen from publicly known documents before the priority date that a plurality of compounds in a scope of general formula (I) of Exhibit Ko 2 may have an activity. Therefore, a person ordinarily skilled in the art could recognize from Exhibit Ko 2 as of the priority date that there is a technical support of the compound of general formula (I) having an HMG-CoA reductase inhibiting activity.

a Exhibit Ko 16, which was publicly known before the priority date, discloses Compounds 2r to 2w as compounds within a scope of general formula (I) of Exhibit Ko 2 having a pharmacophore of an HMG-CoA reductase inhibitor of dihydroxyheptenoic acid structure, and having the same structures in "X" and "A" as the Exhibit Ko 1 Invention. All of these compounds have an HMG-CoA reductase inhibiting activity, which is shown as data (Table I).Further, the production method is also described (page 54 to page 55, left column).

b Regarding the compounds of Working Examples 8 and 23 in the working examples of Exhibit Ko 2 with the same structure in "X" and "A" as the Exhibit Ko 1 Invention, Exhibit Ko 16 and Ko 73 to Ko 75, which were publicly known before the priority date, respectively describe compounds with very similar structures.

In other words, the compound of Working Example 8 of Exhibit Ko 2 is only described as a compound where Compound 2r of "Table I" of Exhibit Ko 16 and Compound 13k of Table 1 of Exhibit Ko 74 have been modified by changing the part of A of the general formula (I) of Exhibit Ko 2 from a methyl ester to a free carboxylic acid or a salt thereof, otherwise described as a compound where a compound at the bottommost of "TABLE 1" of Exhibit Ko 75 has been modified by changing the part of A of general formula (I) of Exhibit Ko 2 from methyl ester of the compound of Working Example 8 of Exhibit Ko 2 to lactone, both of which respectively have

demonstrated an HMG-CoA reductase inhibiting activity. Further, the compound of Working Example 23 of Exhibit Ko 2 is only described as a compound where Compound 2v of "Table I" of Exhibit Ko 16, Compound 13o of Table 1 of Exhibit Ko 74, and Compound I-5-8 of Exhibit Ko 73 have been modified by changing the part of A of general formula (I) of Exhibit Ko 2 from a methyl ester to a free carboxylic acid or a salt thereof, otherwise described as a compound where a compound at the top of "TABLE 1" of Exhibit Ko 75 has been modified by changing the part of A of general formula (I) of Exhibit Ko 2 from methyl ester of the compound of Working Example 8 of Exhibit Ko 2 to lactone, both of which respectively have demonstrated HMG-CoA reductase inhibiting activity.

In view of this publicly known information, it can be recognized that there is all the more technical support of the compound of general formula (I) of Exhibit Ko 2 having an HMG-CoA reductase inhibiting activity.

c Therefore, it can be seen from the publicly known documents before the priority date that a plurality of compounds in the scope of general formula (I) of Exhibit Ko 2 have data showing an activity. Thus it should be found that every compound represented by general formula (I) of Exhibit Ko 2 is a compound in which HMG-CoA reductase inhibiting activity is prima facie expected in the whole scope, similarly to Exhibit Ko 1.

(C) Accordingly, there is a motivation to substitute "dimethylamino group" of Exhibit Ko 1 Invention with "-$N(CH_3)(SO_2CH_3)$" on the basis of the description of Exhibit Ko 2 to obtain a compound of the Invention.

C Motivation from the common general technical knowledge

(A) In view of the common general technical knowledge, a person ordinarily skilled in the art would introduce a hydrophilic group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention and select methylsulfonyl as a hydrophilic group, as mentioned in the aforesaid A(C) and (D).

Further, Exhibit Ko 16 describes the improvement of HMG-CoA reductase inhibiting activity due to the introduction of a bulky lipophilic substituent group at the 2-position of the pyrimidine ring. It fails to disclose, however, that strong HMG-CoA reductase inhibiting activity may not be obtained in the absence of a bulky lipophilic substituent group at the 2-position of the pyrimidine ring. Therefore, the description of Exhibit Ko 16 does not prevent a person ordinarily skilled in the art from

introducing a hydrophilic group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention.

Rather, Exhibit Ko 1 introduces a hydrophilic dimethylamino group at the 2-position of the pyrimidine ring, and thus it was supposed to be a matter of common general technical knowledge that the introduction of a hydrophilic substituent group at the 2-position of the pyrimidine ring would also achieve high activity.

Further, a methylsulfonyl group was a substituent group publicly known as a group imparting hydrophilicity as of the priority date (Figure 6 of Exhibit Ko 60), and a substituent group of which a person ordinarily skilled in the art of drug discovery chemistry would easily conceive.

(B) It is recognized from the description of Exhibit Ko 1 that the Exhibit Ko 1 Invention does not necessarily maintain a current level of HMG-CoA reductase inhibiting activity, supposing a problem to be solved by the Invention to be "to provide a compound having excellent HMG-CoA reductase inhibiting activity to the extent that may become a pharmaceutical product for suppressing the production of cholesterols, or to provide an HMG-CoA reductase inhibitor including the compound as an active ingredient."

In other words, Exhibit Ko 1 describes a result of in vivo cholesterol biosynthesis inhibition test together with in vitro HMG-CoA reductase inhibition test of the Exhibit Ko 1 Invention (a product of Working Example 1b)). According to this, the Exhibit Ko 1 Invention (a product of Working Example 1b)) has an ED_{50} value of 0.028 mg/kg, whereas Mevinolin has an ED_{50} value of 0.41 mg/kg, Compacting has an ED_{50} value of 3.5 mg/kg. It can be seen that the Exhibit Ko 1 Invention has an in vivo activity 15 times as strong as that of Mevinolin (0.41/0.028 = 14.6), and 125 times (3.5/0.028 = 125) as strong as that of Compactin. Mevinolin was commercially available as a hyperlipidemia drug of Lovastatin as of the filing. Compactin was also known as having a drug efficacy sufficient to decrease blood cholesterol in humans (Exhibit Ko 14 and Ko 26). Therefore, the Exhibit Ko 1 Invention does not necessarily maintain a current level of HMG-CoA reductase inhibiting activity for the purpose of solving the above problem, and the problem may be solved even if HMG-CoA reductase inhibiting activity should be decreased by a factor of 125 times. Further, it can be seen that the improvement in pharmacokinetics including the target tissue selectivity of compounds may solve the problem even if the activity is lowered by a factor of more than 125 times.

Therefore, given maintenance of the current level of inhibiting activity, it is

unknown whether the substitution at the 2-position of the pyrimidine ring of the Exhibit Ko 1 Invention may maintain a current level of HMG-CoA reductase inhibiting activity of the Exhibit Ko 1 Invention. Therefore, the determination of the trial decision is erroneous in that it determined lack of motivation to substitute the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention.

Further, in the determination of the support requirement, the trial decision determined by formulating a problem to provide a compound having "excellent HMG-CoA reductase inhibiting activity" to the extent that it may become a pharmaceutical product capable of "suppressing the production of cholesterols" or an HMG-CoA reductase inhibitor including the compound as an active ingredient, whereas in the determination of a motivation with respect to the inventive step, it is determined by formulating a criteria "to maintain a current level of HMG-CoA reductase inhibiting activity of the compound of Exhibit Ko 1 Invention," which goes beyond a level required by the problem to provide a pharmaceutical product "capable of suppressing the production of cholesterols." Thus it is not reasonable to determine support requirement and motivation with such a double standard.

D Summary

Therefore, the determination of the trial decision made an error in that it affirmed the inventive step of Invention 1.

The same can also apply to Inventions 2, 5, and 9 to 12.

E Counterargument against Defendant and Supporting Intervener (hereinafter referred to as "Defendants and others".)

(A) Selection of main cited reference

a Inventive step supposes a person ordinarily skilled in the art and determines whether or not a person ordinarily skilled in the art could have easily conceived of an invention on the basis of the invention disclosed in a distributed publication (Article 29, paragraph (2), Article 29, paragraph (1), item (iii) of the Patent Act).

If Defendant's argument is an argument that a documentarily publicly known invention should not be the only requirement for the selection of main cited reference, and it is not possible without the fact that the publicly known invention had practically constituted a basis for the development by a person ordinarily skilled in the art to raise a document as main cited reference, such argument is equivalent to saying that the state of art should not be established on the basis of a person ordinarily skilled in the

art, but on the actual act of the development, which seems to disregard the literal construction of Article 29, paragraph (2) of the Patent Act that premises publicly known invention provided in Article 29, paragraph (1) for the discussion of inventive step, and introduce a new and different construction in the determination of the inventive step, which might result in the breach of Article 29, paragraph (2).

b Plaintiffs do not fix main cited reference with the Exhibit Ko 1 Invention only in view of the structural similarity to the compound of the Invention. Taking into account that Exhibit Ko 1 discloses that the Exhibit Ko 1 Invention has a high pharmacological activity, the Exhibit Ko 1 Invention is fixed with a main cited reference.

The technical field to which the Invention pertains is directed to a hypercholesteremia drug, more specifically, a statin-based pharmaceutical compound. A person ordinarily skilled in the art has a goal to develop a useful hypercholesteremia drug by creating a statin-based pharmaceutical compound. A person ordinarily skilled in the art has the above goal, and thus he absorbs all information of the publicly known documents before the filing and matters known to researchers in the same field as common general technical knowledge with respect to statin-based pharmaceutical compounds.

Exhibit Ko 1 discloses that the compound of Working Example 1b) (Exhibit Ko 1 Invention) has an in vivo activity 15.8 times that of Mevinolin. It is thus natural for a person ordinarily skilled in the art to focus on a compound of the Exhibit Ko 1 Invention, which is very promising from a viewpoint of activity in a living body.

Therefore, even if it premises the Defendant's understanding of the qualification for the main cited reference, there is no particular problem in the case to fix the main cited reference with the Exhibit Ko 1 Invention.

(B) According to Exhibit Otsu 12 submitted by Defendant, HR780 has a p-fluorophenyl group and an isopropyl group at respective sides of a heterocyclic moiety to which dihydroxyheptenoic acid (or a lactone thereof) binds. Thus, it rather reinforces the argument about the conventional technique presented by Plaintiffs.

In other words, from 10 HMG-CoA reductase inhibitors that were commercially available or developed before the priority date, seven compounds excluding BMY22089 (BMY21950) and Pitavastatin had a p-fluorophenyl group and an isopropyl group at respective sides of a heterocyclic moiety to which dihydroxyheptenoic acid (or a lactone thereof) bound. It was a conventional

technique as of the priority date that a p-fluorophenyl group and an isopropyl group at respective sides of a heterocyclic moiety to which dihydroxyheptenoic acid (or a lactone thereof) bound exhibited excellent HMG-CoA reductase inhibiting activity.

(C) Defendant's argument on the basis of Exhibit Ko 7 about the correlation between liver selectivity and hydrophilicity only picks up an exceptional result, and is not reasonable as set forth below.

a It can be seen from Exhibit Ko 84 (Exhibit Otsu-15) that the compounds such as Lovastatin and Simvastatin, in which a dihydroxyheptenoic acid moiety essential for HMG-CoA reductase inhibiting activity is a lactone body, is effectively transported to the liver and metabolized and converted into an active main body of dihydroxyheptenoic acid, and thus the compound selectively accumulates in the liver; i.e., an HMG-CoA reductase inhibitor having a lactone body is effectively transported to the liver when administered to a living body, and thus is liver-selective. It can be recognized that only Pravastatin is a compound having (an active moiety of) dihydroxyheptenoic acid structure in the compounds tested in Exhibit Otsu 11 (and Exhibit Otsu 12 where its structural formula is described for reference) and Otsu-19 (Exhibit Ko 85), and all of Lovastatin, HR780, and Simvastatin are compounds in which a dihydroxyheptenoic acid moiety is (a prodrug of) a lactone body.

The tests of Exhibit Otsu 11 (Otsu 12) and Exhibit Otsu 19 (Exhibit Ko 85) are the test systems that are inherently unable to detect the effect of hydrophilicity of compound against liver selectivity, because the lactone bodies administered to a rat living body of Lovastatin, HR780, and Simvastatin are effectively transported to the liver due to lactone body and become liver-selective.

Therefore, it cannot be deduced from Exhibit Otsu 11 (Exhibit Otsu 12) and Exhibit Otsu 19 (Exhibit Ko 85) that there is no correlation between hydrophilicity and tissue selectivity.

b Exhibit Otsu 13 was not a publicly known document before the priority date.

c In addition, Exhibit Ko 7 is cited by Exhibit Ko 83, and the inventor of the compound of the Invention himself created the compound of the Invention by introducing a hydrophilic substituent group with reference to Exhibit Ko 7. Thus, Exhibit Ko 7 constitutes common general technical knowledge before the priority date.

(D) As set forth below, it was common general technical knowledge as of the priority date that the order of the degree of inhibiting activity varies depending on the test.

a Data in the table of Exhibit Ko 31 was cited by an article (Exhibit Ko 83) in which the inventor of the compound of the Invention had published his research. Thus, it is a test result implemented before the priority date, and represents a technique itself as of the priority date.

b The order of the degree of inhibiting activity of Fluvastatin and Lovastatin is changed between Exhibit Ko 7 and Ko-8. The order of the degree of inhibiting activity of Pravastatin and Lovastatin is changed between Exhibit Ko 31 and Ko 7. The order of the degree of inhibiting activity of Rosuvastatin salt and BMY-21950 is changed between Exhibit Ko 7 and Ko 15.

c Therefore, it was common general technical knowledge as of the priority date that the order of the degree of inhibiting activity varies depending on the test.

(E) The argument on the basis of domestic records (Exhibit Otsu 21 to Otsu 27) of Sand is not reasonable, because these records were not publicly known as of the filing.

(F) It can be seen from Exhibit Ko 16 that "increased lipophilicity results in a significant increase of inhibiting activity"; however, this does not lead to the finding that "the shift to hydrophilicity results in a significant decrease of activity."

For example, in "Table I" of Exhibit Otsu 17, when CLOGP is calculated as an indicator of lipophilicity for each compound in which a substituent group is introduced, and the compounds are listed in the order of higher to lower lipophilicities, its relative activity (relative (CSI) efficacy) is described as in the following.

No.	R	CLOGP	Relative (CSI) efficacy	Descending order of lipophilicity	Descending order of relative (CSI) efficacy
30	1-naphthyl	5.166	19.6	1	5
26	4-methylphenyl	4.491	49.0	2	4
25	4-fluorophenyl	4.208	62.0	3	3
28	4-methoxyphenyl	4.155	75.8	4	2
29	benzyl	4.011	12.6	5	6
10	phenyl	3.992	83.0	6	1
27	4-tolylsulfonyl	2.782	4.5	7	7

With increasing lipophilicity from the compound of No. 10 in the above table where R is a phenyl to the compound where R is 1-naphthyl, the inhibiting activity generally gets lowered; i.e., it can be recognized that "as the lipophilicity increases from the compound where R is phenyl, the inhibiting activity lowers."

However, with increasing hydrophilicity from the compound (10) where R is a phenyl to a compound (27) where R is 4-trisulfonyl, the inhibiting activity lowers. Therefore, it is erroneous understanding that "imparting hydrophilicity may increase inhibiting activity."

Since hydrophilicity and lipophilicity are relative indicators, the Defendant's argument of if "high lipophilicity results in a significant increase of inhibiting activity," then "hydrophilicity results in a significant decrease of activity" is not reasonable.

Rather, Exhibit Ko 1 shows that the compound of the Exhibit Ko 1 Invention (Compound of Working Example 1b)) and the compound of Working Example 11d exhibited strong HMG-CoA reductase inhibiting activity due to the introduction of hydrophilic amine at the 2-position of the pyrimidine ring (see test A and test B of Exhibit Ko 1).

Therefore, there is no disincentive in Exhibit Ko 16 to introduce a hydrophilic group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention, but it is rather natural for a person ordinarily skilled in the art to conceive of introducing a hydrophilic group at the 2-position of the pyrimidine ring in view of Exhibit Ko 1 etc.

(G) The compound of Exhibit Otsu 17 (Exhibit Ko 76) is a compound with a pyrazole skeleton. Thus the description of the structure-activity relationship by the

substitution of a nitrogen atom of the pyrazole ring in Exhibit Otsu 17 does not provide any suggestion to modify the compound of the Exhibit Ko 1 Invention.

(H)a Plaintiff X argues in the written request for trial (Exhibit Ko 79) that "Substituted pyrimidine compound of general formula (I) of Exhibit Ko 2 has technical support. A person ordinarily skilled in the art would expect an excellent HMG-CoA reductase inhibiting effect for the compound of the Invention where dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention is substituted with a methylsulfonyl group. Therefore, there is a motivation to substitute a dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a methylsulfonyl group.", and also argues that " Exhibit Ko 16 shows data of HMG-CoA reductase inhibiting activity of the compound of formula (I) of Exhibit Ko 2." Therefore, taking into account the fact that it is the compound of general formula (I) of Exhibit Ko 2, for which Exhibit Ko 16 has confirmed pharmacological activity, the compound of general formula (I) of Exhibit Ko 2 has a technical support. The substitution of a dimethylamino group at the 2-position of the pyrimidine ring of the Compound of the Exhibit Ko 1 Invention maintains the activity. Therefore, there is a motivation for such a substitution.

In response to the argument, the trial decision determined that "Since there is no description of the production method or pharmacological activity, it cannot be said that a person ordinarily skilled in the art could conceive of replacing a specific substituent group of the Exhibit Ko 1 Invention on the basis of the description of Exhibit Ko 2 without such a technical support." Thus this argument was considered in the trial proceeding.

b The argument of "Both the compound of Invention 1 and the compound of the Exhibit Ko 1 Invention are selection inventions of the compound of general formula (I) of Exhibit Ko 2," which was presented by Plaintiffs , means that a motivation should not be negated on the presumption that "activity might possibly be lost" when the structure activity relationship of compounds has been clarified at a high level and a number of analogous compounds actually having an activity (equivalent to or higher than that of Mevinolin) have been known, but should be rather affirmed on the presumption that one can "reasonably expect an activity" in accordance with the concept of selection invention. From the viewpoint of the effects, this means that the maintenance of the effects is not a sufficient condition for advantageous effects on the presumption that "activity might possibly be lost," but the significantly high effects

compared to those of the cited invention are a sufficient condition for advantageous effects on the presumption that one can "reasonably expect an activity" in accordance with the concept of selection invention.

The argument by Plaintiffs does not change the primarily cited reference, but poses a question about the determination criteria of the inventive step that was considered in the proceeding of the trial.

c Plaintiff X argues in the written request for trial (Exhibit Ko 79) that "Patentee misunderstood that the compound Ia-1 of the Invention (the compound of Invention 1) had a significantly high activity compared to the conventional technique, and completed 'the patent invention' and described the Detailed Description of the Invention of the specification." "The patent invention" used herein is a comprehensive expression of "the invention recited in the claims according to the request for an invalidation trial" (Exhibit Ko 79, page 2, lines 10 to 11), and thus includes the whole range of the compounds of Claim 1 of the Patent.

Therefore, Plaintiff X did not only present an argument that the calcium salt of the compound Ia-1 of the specification was not supported among the compounds of Invention 1. The argument in this case to the effect that the whole range of the compound of the Invention 1 is not supported does not correspond to the addition of the argument.

(2) Errors in the determination of the effect of the Invention

A There is a motivation to conceive of the compound of the Invention from Exhibit Ko 1 and Ko 2. Therefore, it is necessary for the compound of the Invention to cause significant effects unexpected from Exhibit Ko 1 and Ko 2 in view of the common general technical knowledge to involve an inventive step, but such significant effects are not found.

Further, given that the Invention 1 is a selection invention of the compound of the general formula (I) of Exhibit Ko 2, it is all the more necessary to perform significant activity compared to a compound out of the selected range.

B As set forth below, the effects of Invention 1 should be compared with those of the compound of the Exhibit Ko 1 Invention. Thus the determination of the trial decision is erroneous in that it affirmed the effects of Invention 1 by comparing the effects of sodium Mevinolin with the effects of Invention 1.

(A) Prior to the priority date, there were developed and commercially

available HMG-CoA reductase inhibitors having a hexahydronaphthalene skeleton such as Lovastatin, Simbastatin, and Pravastatin. A number of HMG-CoA reductase inhibiting compounds in which the hexahydronaphthalene was converted into another skeleton were publicly known (Exhibit Ko 8).

There were numerous reports before the priority date on the HMG-CoA reductase inhibiting compound of the Invention in which hexahydronaphthalene was converted into pyrimidine (Exhibit Ko 1, Ko 2, Ko 16, and Ko 73 to Ko 75). Among them, the compound of the Exhibit Ko 1 Invention has a very similar structure to the compound of Invention 1. The structural difference was only a methyl group (the compound of the Exhibit Ko 1 Invention) or an alkylsulfonyl group (the compound of Invention 1) binding to amine at the 2-position of the pyrimidine ring.

(B) Both the compound of the Exhibit Ko 1 Invention and the compound of the Invention are included in general formula (I) of Exhibit Ko 2. It is thus a so-called selection invention of the compound of general formula (I) of Exhibit Ko 2 (setting aside whether the effects are significant, it is the case where the compound falls within the scope of the general formula of the patent specification of an earlier application, but the patent specification of the earlier application fails to describe the specific compound).

The selection invention is at least required to have a significantly high HMG-CoA reductase inhibiting activity compared to the compound of the Exhibit Ko 1 Invention that was a specific publicly known compound falling within the scope of general formula (I) of Exhibit Ko 2, not compared to sodium Mevinolin, in order to find the inventive step of the compound of Invention 1 over the Exhibit Ko 2 Invention which constitutes the above concept.

(C) Patentee had known of the existence of Exhibit Ko 1 and Ko 2 before the filing of the U.S. application having the same content and being filed at almost the same time as the application of this case, and thus had known of Exhibit Ko 1 and Ko 2 as of the filing, and had recognized that the compound of Invention 1 and the compound of the Exhibit Ko 1 Invention were selection inventions of the Exhibit Ko 2 Invention. Further, the Patentee had also recognized that the compound of Invention 1 needed to cause a significant HMG-CoA reductase inhibiting activity compared to the compound of the Exhibit Ko 1 Invention in order to find the inventive step of the compound of Invention 1 over the Exhibit Ko 2 Invention.

It is believed that the Patent was established by preparing the specification as if

the Patentee had not known that the Invention was a selection invention, regardless of the recognition of the Invention being a selection invention as of the filing, and, in response to the assertion of lack of inventive step in the notice of reasons of refusal, deliberately submitting data showing unreliably high effects in a written opinion, and demonstrating that the significant effects qualified for the selection invention compared to the compound of the Exhibit Ko 1 Invention to obtain a decision to grant a patent.

If the standard for comparison of the effects of the compound of Invention 1 should be recognized as sodium Mevinolin, not a compound of the Exhibit Ko 1 Invention after the registration of the Patent and the determination should be made to the effect that "it does not necessarily require a higher HMG-CoA reductase inhibiting effect compared to the Exhibit Ko 1 Invention," this might endorse the way of tentatively acquiring a patent by arguing an inventive step on the basis of extremely unreliable data, instead of presenting an argument about the effects on the basis of reliable data in the written opinion against a notice of reasons of refusal without the description of comparative data on the effects with a compound having the most analogous structure in the specification of the application.

C As set forth below, even if it were appropriate to compare the compound of Invention 1 with sodium Mevinolin, it cannot be deduced from the description of the specification that the compound of Invention 1 has a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin.

(A) A person ordinarily skilled in the art fails to understand what the numerical values of Table 4 in the specification mean.

The specification describes a method for the measurement and an assay result of HMG-CoA reductase inhibiting activity of the compound of Invention 1. It discloses that "the activities of the compounds of the Invention measured by the method are shown in Table 4 as comparative data, based on the assumption that the inhibiting activity of Mevinolin (sodium salt) as the reference drug is 100" ([0042]), and Table 4 shows data of relative activity of the test compound.

The pharmacological activity of the compound is specifically shown only in Table 4 in the specification. In the table, HMG-CoA reductase inhibiting activities of compounds Ia-1, Ia-3, Ia-5, and Ia-7 are shown by use of rat liver microsome; however, the compound likely to support Invention 1 is only compound Ia-1. Table 4 discloses that compound Ia-1 has a relative activity of 442 with the inhibiting activity of sodium Mevinolin given as 100.

However, the inhibiting activity varies depending on the condition, mainly the concentration of compound. A person ordinarily skilled in the art fails to understand from the description of "on the assumption that the inhibiting activity of Mevinolin (sodium salt) as the reference drug is 100" in what condition the inhibiting activity of Mevinolin (sodium salt) was set to 100.

For example, a person ordinarily skilled in the art fails to understand which of the following is true: a) Measurement was made for the inhibiting activity of Mevinolin (sodium salt) at a certain level of concentration, and given the activity be 100, a relative value of inhibiting activity of test compound at the same concentration was shown in Table 4, or b) Measurement was made for the inhibiting activity of Mevinolin (sodium salt) at two or more levels of concentration, and from the results the IC_{50} value of inhibiting rate of test compound was calculated, and given the value be 100, a relative value of IC_{50} value of test compound was shown in Table 4, or other another procedure was made.

Further, for example, when the HMG-CoA reductase inhibiting activity is 1%, 50%, and 90%, respectively for 1 nM, 10 nM, and 100 nM of the compound A, and the HMG-CoA reductase inhibiting activity is 5%, 30%, and 50% respectively for 1 nM, 10 nM, and 100 nM of the compound B, given that the HMG-CoA reductase inhibiting activity for 1 nM of the compound A (1%) is 100, the HMG-CoA reductase inhibiting activity for 1 nM of the compound B is 5%. Therefore, the activity of the compound B relative to the compound A is 500 in the case of the above b). On the other hand, the compound A has an IC_{50} value of 10 nM, and the compound B has an IC_{50} value of 100 nM. Therefore, in the case of the above a), a relative activity of the IC_{50} value of the compound B is 10, given that the IC_{50} value of the compound A is 100. In other words, the order of the degree of activity of the compounds is reversed between the case of the above a) and the case of the above b), and the order of the degree of activity of the compounds cannot be understood unambiguously.

(B) It was known as of the filing that the method for the measurement of in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome described in the specification caused varied results, and the order of the degree of inhibiting activity also varied (Exhibit Ko 7, Ko 8, Ko 31, Ko 35, Ko 75). Therefore, a person ordinarily skilled in the art fails to understand which of the compounds has a higher inhibiting activity and which of the compounds has a lower inhibiting activity unless the results of implementing at least multiple separate same experimentations are shown. The result of Table 4 is only a measurement result for one time (Exhibit Ko 5), and it

cannot be thus deduced for a person ordinarily skilled in the art from the description of the specification that the compound of the Invention 1 has a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin.

Most patent applications for HMG-CoA reductase inhibiting compound having a pyrimidine skeleton did not demonstrate the HMG-CoA reductase inhibiting activity of a compound by showing data of a one-time test result of only one kind of test of in vitro HMG-CoA reductase inhibiting test by use of liver microsome like the Patent (Exhibit Ko 1, Ko 73, Ko 74, Ko 77, Ko 78). This fact supports the recognition of a person ordinarily skilled in the art that results for one kind and one-time test system are not sufficient, but results of a plural kinds of tests must be shown as data in view of the variation of test results in the discussion about the degree of HMG-CoA reductase inhibiting activity among compounds.

D As set forth below, Exhibit Ko 3 fails to support the fact that the Invention 1 has a significant effect.

(A) It cannot be seen from the documents submitted after the filing that a person ordinarily skilled in the art could not understand from the specification. Therefore, the determination of the trial decision to the effect that "Exhibit Ko 3 supports the significant effects of the Invention 1. Therefore, the effects of the Invention 1 cannot be negated" is erroneous.

(B) Data of S-4522 (Invention 1) and SDZ-65129 (Exhibit Ko 1 Invention) of Exhibit Ko 3 summarize the results of the measurements 1 to 3 of Exhibit Ko 5. It can be seen that these data had been obtained by August 1, 1996. Exhibit Ko 3 and Ko 5 disclose that compound Ia-1 of the specification has in vitro HMG-CoA reductase inhibiting activity only about two times higher than that of the compound of Working Example 1b) of Exhibit Ko 1. They fail to describe activity about nine times higher.

Patentee submitted the written amendment and the written opinion on August 12, 1996 in response to the reason for refusal due to the lack of novelty and the lack of inventive step with Exhibit Ko 1 as a cited document, in an attempt to overcome the lack of novelty and the lack of inventive step to obtain a decision to grant a patent. In the above written opinion, Patentee argued that compound Ia-1 of the specification had an in vitro HMG-CoA reductase inhibiting activity about nine times higher than that of the compound of Working Example 1b) of Exhibit Ko 1, and was thus particularly superior.

Patentee did not submit experimental results allegedly having about two-time activity that he should have recognized as reliable results as of the submission of the above written opinion, but submitted an experimental result allegedly having about nine-time activity, and only argued about the significant effects of the compound of Invention 1 (without the argument about the structure) in an attempt to overcome the reasons for refusal due to lack of inventive step. Therefore, Patentee actually admitted that the significant effects did not mean "about two-time activity," but meant "about nine-time activity" compared to the compound of the Exhibit Ko 1 Invention. At this late date, this is not permitted because of estoppel and the violation of fair and equitable principle to argue that the significant effects may be even caused by "about two-time activity," and that "about nine-time activity" is not a requirement for the significant effects.

Further, Patentee had known as of the submission of the above written opinion that the patentability might not be ensured unless Invention 1 caused significant effects as a selection invention of Exhibit Ko 2 Invention. Therefore, it is believed that he argued about significant effects sufficient for patentability. The above argument is all the more not permitted due to estoppel.

E As set forth below, the description fails to disclose that Invention 1 has a significant effect.

(A) The compound of the Exhibit Ko 1 Invention having a very similar structure to the compound of Invention 1 falls within the scope of the general formula (I) of Exhibit Ko 2, but is out of the scope of Invention 1. Taking into account the IC_{50} value (0.068 μM) of the HMG-CoA reductase inhibiting activity of sodium Mevinolin described in Table 1 of Exhibit Ko 8 and the IC_{50} value (0.026 μM) of HMG-CoA reductase inhibiting activity as a result of test A of Exhibit Ko 1, it could be presumed that the compound of the Exhibit Ko 1 Invention would have an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome 2.6 times higher than that of sodium Mevinolin.

Further, compounds 2t, 2u, 2v and 2w of Exhibit Ko 16 are compounds falling within the scope of general formula (I) of Exhibit Ko 2, but are out of the scope of Invention 1. These compounds have an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome 2.6 to 8 times higher than that of sodium Mevinolin (Compound 1b of Exhibit Ko 16).

(B) However, it is failed to describe anywhere in the description and it

cannot be seen from anywhere in the description that the compound of Invention 1 from which its high HMG-CoA reductase inhibiting activity compared to sodium Mevinolin cannot even be seen had had significant activity (sufficiently significant activity compared to the compound of the Exhibit Ko 1 Invention and compounds 2t, 2u, 2v and 2w of Exhibit Ko 16) appropriate for a selection invention of the Exhibit Ko 2 Invention in view of Exhibit Ko 1 and Exhibit Ko 2, which describes the general formula of the above concept of Exhibit Ko 1.

(C) Referring to Exhibit Ko 3, which is a document after the filing, Exhibit Ko 3 shows that S-4522 (Rosuvastatin), a calcium salt of compound Ia-1 of Table 4 of the description, has an activity 2.0 times higher than that of sodium Mevinolin according to the measurement results of HMG-CoA reductase inhibiting activity obtained by multiple measurements. Therefore, it can only be seen from Exhibit Ko 3 that compound Ia-1 has about two-times higher the activity of sodium Mevinolin.

On the other hand, the compounds of Exhibit Ko 16 (2t, 2u, 2v and 2w) and the compound of the Exhibit Ko 1 Invention falling within general formula (I) of Exhibit Ko 2 and out of Invention 1 might have or might be expected to have an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome 2.6 to 8 times higher than that of sodium Mevinolin.

Therefore, even if Exhibit Ko 3 should be considered, it is not supported in view of Exhibit Ko 1 and Ko 2 that the compound of the Invention 1 had had a sufficiently significant activity.

(D) The trial decision determined that "Whether or not the Invention causes significant effects should be determined with a criterion of whether or not to expect the effect of the Invention from the Exhibit Ko 1 Invention and the common general technical knowledge as of the priority date. The Invention needs not necessarily have a high HMG-CoA reductase inhibiting activity compared to the Exhibit Ko 1 Invention." In view that both the Exhibit Ko 1 Invention and Invention 1 were selection inventions of the Exhibit Ko 2 Invention, the determination of the above trial decision is erroneous.

F Summary

Therefore, the effects are not considered. From this viewpoint, it is not supported that Invention 1 involves an inventive step over Exhibit Ko 1 and Ko 2.

The same can also apply to Inventions 2, 5, and 9 to 12.

2 Ground 2 for rescission (Errors in the determination of the support requirement)

(1) Finding of a problem to be solved by Invention 1

A As set forth below, the problem found in the trial decision is inappropriate in view of the common general technical knowledge as of the filing.

(A) What was found first as a compound having "excellent HMG-CoA reductase inhibiting activity" to the extent that may become a pharmaceutical product is Compactin (Exhibit Ko 14, Ko 26). Compactin had been already publicly known more than a decade before the filing of the Patent (Exhibit Ko 66).

It is inappropriate to formulate a problem to be solved by the Invention "to provide an HMG-CoA reductase inhibitor including a compound having 'excellent HMG-CoA reductase inhibiting activity' or the compound as an active ingredient to the extent that may become a pharmaceutical product for 'suppressing the biosynthesis of cholesterols'" at the same level as the state of art more than a decade before.

(B) As of the filing date of the patent, there were already a plurality of HMG-CoA reductase inhibitors in the market as pharmaceutical products.

Further, a plurality of the compounds with a pyrimidine skeleton, which was the same as the Invention 1, were publicly known (Exhibit Ko 16, and Ko 73 to Ko 75), and a compound showing a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin was also publicly known (Exhibit Ko 16).

In view of such common general technical knowledge as of the filing, "the extent that may become a pharmaceutical product for 'suppressing the biosynthesis of cholesterols'" in the problem formulated by the trial decision is a lower level compared to the common general technical knowledge, and thus inappropriate.

B As set forth below, the problem formulated by the trial decision is inappropriate in view that the compound of Invention 1 is a compound within the scope of general formula (I) of Exhibit Ko 2.

(A) Invention 1 includes the scope of general formula (I) of Exhibit Ko 2. If the compound of Invention 1 should have patentability (in particular inventive step) in such circumstances, it would be the case of a selection invention. If so, the compound of Invention 1 needs to have a significant effect over the other compounds of general formula (I) of Exhibit Ko 2.

Here, compounds 2t, 2u, 2v and 2w of Exhibit Ko 16 are compounds falling within the scope of general formula (I) of Exhibit Ko 2, but out of the scope of

Invention 1. These compounds were publicly known as of the filing to have an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome 2.6 to 8 times higher than that of sodium Mevinolin (Compound 1b) of Exhibit Ko 16) (Exhibit Ko 16).

Further, the compound specifically described as Working Example 23 of Exhibit Ko-2 is a methyl ester of carboxylic acid of compound 2v of Exhibit Ko 16, and a compound having HMG-CoA reductase inhibiting activity comparable to a so-called prodrug of compound 2v of Exhibit Ko 16. It can be seen that Exhibit Ko 2 had described a compound having a HMG-CoA reductase inhibiting activity 2.6 times higher than that of sodium Mevinolin (the activity of the compound 2v of Exhibit Ko 16 is 2.6 times higher than that of sodium Mevinolin (the compound 1b of Exhibit Ko 2)) as a specific compound in the working examples.

(B) The compound of the Exhibit Ko 1 Invention having a very similar structure to the compound of Invention 1 also falls within the scope of general formula (I) of Exhibit Ko 2, but out of the scope of Invention 1. Taking into account the IC_{50} value (0.068 μM) of HMG-CoA reductase inhibiting activity of sodium Mevinolin described in Table 1 of Exhibit Ko 8 and the IC_{50} value (0.026 μM) of HMG-CoA reductase inhibiting activity as a result of test A of Exhibit Ko 1, a person ordinarily skilled in the art could presume as of the filing that the compound of the Exhibit Ko 1 Invention would have an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome, 2.6 times higher than that of sodium Mevinolin.

(C) As seen above, what was publicly known as of the filing was the compound having an in vitro HMG-CoA reductase inhibiting activity by use of rat liver microsome 2.6 to 8 times higher than (or reasonably expected to be higher than) that of sodium Mevinolin in the compounds encompassed into general formula (I) of Exhibit Ko 2.

Therefore, in order that the compound of Invention 1 may involve an inventive step in view of the compound of general formula (I) of Exhibit Ko 2, it is contemplated that the compound needs to have an HMG-CoA reductase inhibiting activity 2.6 to 8 times higher than that of sodium Mevinolin.

(D) Exhibit Ko 1 describes the result of an in vivo cholesterol biosynthesis inhibiting test using rat, and shows that Compactin has an in vivo cholesterol biosynthesis inhibiting effect about 8.5 times lower than that of Mevinolin (3.5/0.41 =

8.53).

Compactin was a publicly known, and authorized HMG-CoA reductase inhibitor, and was known to have a drug efficacy sufficient to lower blood cholesterol in human (Exhibit Ko 14, Ko 26). Therefore, it can be recognized that a problem formulated by the trial decision "to provide a compound having 'excellent HMG-CoA reductase inhibiting activity' to the extent that may become a pharmaceutical product for 'suppressing the biosynthesis of cholesterols'" may be solved, even if Compactin had an HMG-CoA reductase inhibiting activity about 8.5 times lower than that of Mevinolin.

Consequently, it can be recognized that a problem formulated by the trial decision may be solved by Compactin that has an HMG-CoA reductase inhibiting activity about 8.5 times lower than that of sodium Mevinolin.

However, in order that the compound of Invention 1 may involve an inventive step as a selection invention in view of the compound of general formula (I) of Exhibit Ko 2, it can be seen that the compound needs to have an HMG-CoA reductase inhibiting activity 2.6 to 8 times or more higher than that of sodium Mevinolin. Therefore, even if the problem formulated by the trial decision should be solved, it may not involve an inventive step as a selection invention, and thus the invention cannot be granted a patent.

As seen above, even if the problem formulated by the trial decision should be solved, it may not involve an inventive step and thus cannot be a patented invention. This is only because the problem formulated by the trial decision is of a significantly low level relative to the common general technical knowledge at that time, and thus inappropriate.

C As set forth below, the problem formulated by the trial decision is inappropriate in view of the situation as of the filing.

Patentee had recognized Exhibit Ko 1 and Ko 2 as of the filing (May 28, 1992), and that the compounds of Invention 1 and the Exhibit Ko 1 Invention fell within the scope of general formula (I) of Exhibit Ko 2.

Given such recognition, regardless of Exhibit Ko 1 describing compound 1b) (Compound of the Exhibit Ko 1 Invention) showing an in vivo strong HMG-CoA reductase inhibiting activity comparable to that of Mevinolin (may have the same activity as sodium Mevinolin metabolized in a living body), it is unlikely to formulate a problem to be solved by the Invention "to provide an HMG-CoA reductase inhibitor including a compound having 'excellent HMG-CoA reductase inhibiting activity' or the

compound as an active ingredient to the extent that it may become a pharmaceutical product for 'suppressing the biosynthesis of cholesterols,'" which may be solved even by a compound with an HMG-CoA reductase inhibiting activity about 8.5 times lower than that of sodium Mevinolin.

D Therefore, the problem of the Invention formulated by the trial decision is incorrect.

(2) A person ordinarily skilled in the art fails to recognize that Invention 1 may solve a problem "to provide a compound having an excellent HMG-CoA reductase inhibiting activity"

A A plurality of HMG-CoA reductase inhibitors having pyrimidine skeleton like Invention 1 were known as of the filing date of this case (Exhibit Ko 1, Ko 2, Ko 73 to Ko 75). Among them, compounds having an HMG-CoA reductase inhibiting activity 2.6 to 8 times higher than that of sodium Mevinolin were publicly known, like the compounds 2t to 2w of Exhibit Ko 16.

Further, regarding the compound of the Exhibit Ko 1 Invention, taking into account the IC_{50} value (0.068 μM) of HMG-CoA reductase inhibiting activity of sodium Mevinolin described in Table 1 of Exhibit Ko 8 and the IC_{50} value (0.026 μM) of HMG-CoA reductase inhibiting activity as a result of test A of Exhibit Ko 1, a person ordinarily skilled in the art could presume as of the priority date that the compound of the Exhibit Ko 1 Invention would have an HMG-CoA reductase inhibiting activity 2.6 times higher than that of sodium Mevinolin. Furthermore, according to Defendant's argument, the compound of Working Example 11d of Exhibit Ko 1 is allegedly a compound having a higher activity as compared to the compound of the Exhibit Ko 1 Invention if a racemic body thereof is divided into a single enantiomer.

In such circumstances where there is common general technical knowledge, and the test result of activity measurement described in the description varies so that the order of the degree of activity sometimes switches, the average value and the standard deviation are not shown, but only a one-time test result with sodium Mevinolin (positive control) is shown, which can be seen from the disclosure of Table 4 in the description. It cannot be seen from the disclosure that a compound with "excellent" HMG-CoA reductase inhibiting activity is disclosed. The description fails to disclose that Invention 1 has a strong HMG-CoA reductase inhibiting activity comparable to that of sodium Mevinolin.

Further, the description does not disclose anywhere that the compound of Invention 1 causes significant effects in view of Exhibit Ko 1 and Ko 2.

A person ordinarily skilled in the art may not recognize from such content of the description that a problem of Invention 1 "to provide a compound having an excellent HMG-CoA reductase inhibiting activity" may be solved.

B The compound of the Invention is a selection invention of general formula (I) of Exhibit Ko 2, and its structure has already been disclosed. Thus, the identification of the structure is not at all the disclosure of a novel technique.

The description only discloses activity that cannot be said to be significant in comparison to sodium Mevinolin, which is only a positive control (measurement for a standard compound to be measured for verifying the normality of each measurement and comparing test results between measurements) regarding a compound with identified structure. Therefore, the description fails to disclose any novel technique.

C Plaintiff X pointed out in the written request for trial (Exhibit Ko 79) the Patentee's dishonest behavior to obtain a decision to grant a patent by submitting self-serving data of compound Ia-1 of the description having about 9 times higher activity in the written opinion of the prosecution of the Patent (Submitted on August 12, 1996. Exhibit Ko 6.), regardless of his knowledge of the compound having only two-times higher activity than the compound of the Exhibit Ko 1 Invention, and argued about the nonconformance to so-called support requirement.

In contrast, Patentee argued in the written reply (Exhibit Ko 80) that "The Correction has rendered compound Ia-1 (corresponding to the sodium salt of Rosuvastatin) out of the scope of claims. Accordingly, the argument in the written request for invalidation trial on the basis of data of the compound Ia-1 in the written opinion (Exhibit Ko 6) is no longer an argument of the noncompliance of support requirement"; i.e., "Data of compound Ia-1 do not support the Corrected Invention (the Invention). Thus there is no room to doubt the conformance to the support requirement, regardless of whether or not the Examiner misunderstands that the activity of compound Ia-1 is high."

This is the Patentee's admission that Invention 1 is not supported by data of compound Ia-1 of the description. The description lacks any other data of HMG-CoA reductase inhibiting activity that supports Invention 1. Therefore, it cannot be recognized that a person ordinarily skilled in the art may recognize that a problem to be solved by the Invention "to provide a compound having an excellent HMG-CoA

reductase inhibiting activity" may be solved.

(3) A person ordinarily skilled in the art could not understand that the overall range of compounds of the Invention 1 had higher activity compared to sodium Mevinolin

A person ordinarily skilled in the art could understand that compound Ia-1 described in the description had a higher activity compared to sodium Mevinolin, but could not understand that the overall range of compounds of the Invention 1 had higher activity compared to sodium Mevinolin.

In other words, for example, when the isopropyl group at the moiety corresponding to R^3 of formula (I) of Invention 1 in compound Ia-1 (compound 2t of Exhibit Ko 16) is substituted with a methyl group (the compounds 2r, 2s of Exhibit Ko 16), it is inferred from the comparison between 2r to 2s and 2t to 2w of Exhibit Ko 16 that HMG-CoA reductase inhibiting activity is lowered by a factor of 100 times or more. Therefore, it can be said that the substitution of an isopropyl group with a methyl group results in the decrease of activity by a factor of 100 times or more. It cannot be seen from the common general technical knowledge as of the filing that, although compound Ia-1 has an HMG-CoA reductase inhibiting activity 4.42 times higher than that of sodium Mevinolin, the whole range of the compounds of the Invention 1 has HMG-CoA reductase inhibiting activity higher than that of sodium Mevinolin like compound Ia-1.

In addition, compounds 2r to 2s and compounds 2t to 2w of Exhibit Ko 16 are different from each other in that the moiety corresponding to "-X-R^1" of formula (I) of Invention 1 is isopropyl (i-C_3H_7), etc. for 2t to 2w and a methyl group (CH_3) for 2r to 2s.

However, the above difference is presumed to reduce HMG-CoA reductase inhibiting activity by a factor of about three times at most when comparing compound 2f and compound 2e of Exhibit Ko 16, both of which are compounds with a pyridine skeleton. Most of the reduction in HMG-CoA reductase inhibiting activity may be attributed to the difference in the above R^3. Therefore, the difference in the moiety corresponding to -X-R^1 does not contribute to the reduction of HMG-CoA reductase inhibiting activity by a factor of more than 100 times.

(4) Summary

Therefore, it cannot be seen for a person ordinarily skilled in the art from the description of the Detailed Description of the Invention that the problem to be solved

might be solved by Invention 1, and thus the determination of the trial decision that affirmed the conformance to the support requirement is erroneous.

Further, regarding the aforesaid items (1) and (2), the same can also apply to Inventions 2, 5, and 9 to 12. Therefore, the determination of the trial decision that affirms the conformance to the support requirement for these Inventions is erroneous.

No. 6 Argument by Defendant and others

1 Ground 1 for rescission

(1) Selection of primarily cited reference

A(A) The compound of the Exhibit Ko 1 Invention that Plaintiffs see as a so-called lead compound in the primarily cited reference was selected as the most analogous compound in structure to the compound of the subject of the Invention with the knowledge of the content of the Invention in hindsight.

If there is no reasonable reason other than the similarity of structure to the Invention in hindsight to select a lead compound in the primarily cited reference, a person ordinarily skilled in the art would not easily conceive of the selection itself of the primarily cited reference. That is enough to establish an inventive step.

Plaintiffs fail to show any reasonable reason other than the similarity of the structure of the Invention in hindsight for the selection of the compound of Exhibit Ko 1 Invention as a lead compound. Therefore, the Invention is construed as involving an inventive step without discussing ground 1 for rescission.

(B) At least five competing companies had begun to research and develop a statin with a pyrimidine skeleton by the priority date of the Patent (Exhibit Ko 8, Ko 73); however, none of the companies could place it on the market. The inventors of the Invention made a success in creating a novel compound with the world's highest level of HMG-CoA reductase inhibiting activity through research and development of a statin with a pyrimidine skeleton.

Therefore, the compound of the Exhibit Ko 1 Invention is not appropriate for the lead compound.

Even if a person ordinarily skilled in the art should give importance to the result of the test B of Exhibit Ko 1 as Plaintiffs argued, a single enantiomer of an active body of the compound of Working Example 11d is expected to have a higher activity compared to the compound of the Exhibit Ko 1 Invention from the result of the test B. Therefore, a person ordinarily skilled in the art would select the compound of Working Example 11d, not the compound of the Exhibit Ko 1 Invention, as a lead compound.

B(A) When a primarily cited invention belongs to the category where a person ordinarily skilled in the art ceased to research and develop as of the filing date, the adverse effect of the post-facto analysis cannot be overlooked in specifying the primarily cited invention. Therefore, this situation should be considered in the determination of the difference related to inventive step.

Further, when an inventor should achieve an invention causing superior effects starting from a primarily cited invention in which many persons ordinarily skilled in the art did not show any interest, many persons ordinarily skilled in the art could have recognized that he could not achieve an excellent invention even if one should try to improve starting from the primarily cited invention. Therefore, the effects should be evaluated as beyond expectation.

According to the fact of aforesaid A(B), the effects of the Invention should be evaluated as unexpected and significant ones. Thus the inventive step of the Invention should be affirmed.

If the Exhibit Ko 1 Invention should have superior effects and be suitable for a lead compound as Plaintiffs argue, the Invention should be all the more evaluated as causing unexpected and significant effects, since the Invention causes effects exceeding the Exhibit Ko 1 Invention.

(B) In a lawsuit of the U.S., the inventive step of the U.S. Patent corresponding to the Patent (nonobviousness) was affirmed in comparison to the publicly known documents and an argument of invalidation similar to the trial of the case (Exhibit Otsu 7, Otsu 8).

The determination of inventive step should have elements to be considered in common in each jurisdiction from a viewpoint of international harmonization.

(2) Errors in the determination of lack of motivation

A Motivation from Exhibit Ko 1

(A) It cannot be recognized that the overall range of the compound represented by general formula I of Exhibit Ko 1 has a pharmacological activity similar to that of the Exhibit Ko 1 Invention, and a person ordinarily skilled in the art could not reasonably expect the pharmacological activity for a compound out of the range.

It was a matter of common general technical knowledge as of the priority date that a pharmacological activity might be lost in many cases if a part of a substituent

group of a compound having pharmacological activity is changed (an example of Lovastatin and Pravastatin in Exhibit Ko 7, Exhibit Otsu 65, Otsu 66). Exhibit Ko 1 fails to suggest that the difference 1-i may drastically improve the HMG-CoA reductase inhibiting activity.

(B) Although a compound out of the range of the general formula I of Exhibit Ko 1 might possibly show the HMG-CoA reductase inhibiting activity, one cannot establish that "HMG-CoA reductase inhibiting activity may be expected for all the compounds out of the range of general formula I of Exhibit Ko 1," nor that "HMG-CoA reductase inhibiting activity may be expected for the compound of the Invention among the compounds out of the range of general formula I of Exhibit Ko 1."

A number of the compounds are present out of the range of the general formula I of Exhibit Ko 1. Among them, there are a number of compounds with a poor HMG-CoA reductase inhibiting activity. Exhibit Ko 1 gives no hint as to what compound shows a superior HMG-CoA reductase inhibiting activity.

General formula I of Exhibit Ko 1 fails to comprise the structure of the difference (1-i) (for example, $N(CH_3)(SO_2R')$(R': alkyl group) as a substituent group at the 2-position of the pyrimidine ring).

(C) It was known as of the priority date that liver selectivity did not necessarily have a correlation with hydrophilicity (Exhibit Ko 7, Exhibit Otsu 11 to Otsu 13, Otsu 19), and it was well-known that the hydrophilicity of statin does not have a correlation with HMG-CoA reductase inhibiting activity (Exhibit Ko 7). Therefore, a person ordinarily skilled in the art would not have a motivation to simply improve the hydrophilicity of a statin.

If the argument by Plaintiffs were correct in that the tests of Exhibit Otsu 11 and Otsu 19 are test systems unable to detect the effect of hydrophilicity of a compound on the liver selectivity, since the effect of liver selectivity caused by the hydrophilicity of a compound is hidden by the effect of a lactone body, a person ordinarily skilled in the art who read the results of Exhibit Otsu 11 and Otsu 19 could be motivated to change a compound into a prodrug (lactone body), rather than rendering the compound hydrophilic for the purpose of improving the liver selectivity of a statin. Further, if the above argument were correct, an in vivo test system would be a test system that inherently fails to detect the effect of hydrophilicity of a compound on liver selectivity. Therefore, even if a person ordinarily skilled in the art could recognize from the result of the test B of Exhibit Ko 1 that the compound of

Exhibit Ko 1 Invention had good in vivo activity, he could not understand that it correlated with the improvement of hydrophilicity.

(D) Exhibit Ko 1 lacks description considering the correlation of HMG-CoA reductase inhibiting activity with degree of hydrophilicity. Therefore, it cannot be said that it discloses the correlation of the inhibiting activity of the compounds of Working Example 1b) and Working Example 11b with hydrophilicity of the substituent group at 2-position.

First of all, test B is a test for the measurement of the inhibiting activity of cholesterol biosynthesis, not a test for the measurement of HMG-CoA reductase inhibiting activity.

Even if a person ordinarily skilled in the art would focus on the hydrophilicity of the substituent group, the highly hydrophilic pyridyl group is introduced at the 4-position (4-pyridyl) of the pyrimidine ring of the compound of Working Example 11d, and a person ordinarily skilled in the art could understand that a single enantiomer of an active body of Working Example 11d had a higher activity compared to the compound of the Exhibit Ko 1 Invention. Therefore, a person ordinarily skilled in the art could focus on a substituent group at the 4-position, not the 2-position.

(E) Hydrophilicity is a relative concept, and is determined by comparison between two substituent groups. When the atom -H of an aromatic compound is substituted with a dimethylamino group, it shows hydrophobicity (Exhibit Ko 9). Therefore, it cannot be said that a dimethylamino group is hydrophilic.

(F) Of course, it is naturally an alternative for a person ordinarily skilled in the art to modify both methyl groups of a dimethylamino group with a hydrophilic group having smaller contribution to hydrophilicity compared to a methylsulfonyl group, rather than to modify only one methyl group of a dimethylamino group at the 2-position of the pyrimidine ring with a publicly known hydrophilic group of a methylsulfonyl group.

Besides a methylsulfonyl group, there are many hydrophobic groups having a small contribution (Exhibit Otsu 4). Therefore, there was no motivation to select a methylsulfonyl group among these groups.

(G) The schematic drawing is drawn by Plaintiff as if general formula I of Exhibit Ko 1 and general formula (I) of Exhibit Ko 2 overlap across a wide range, but

actually the overlapping range is limited. Further, the above schematic drawing is drawn as if only the Invention is located in the vicinity of the Exhibit Ko 1 Invention, but actually Exhibit Ko 2 describes a number of substituent groups equivalently as a substituent group at the 2-position of the pyrimidine ring, and thus the schematic drawing by Plaintiffs is misleading.

B Motivation from Exhibit Ko 2

(A)a In the trial, Plaintiff failed to present any argument that Exhibit Ko 2 describes the manufacturing method and HMG-CoA reductase inhibiting activity for the whole range of the compounds of general formula (I) or that Exhibit Ko 16 shows data of HMG-CoA reductase inhibiting activity for a compound of general formula (I) of Exhibit Ko 2, none of which was a subject for trial examination. Therefore, it is not permitted for Plaintiffs to present in this lawsuit the argument of the aforesaid No. 5, 1(1)B, and the argument about the error in the determination to the effect that there is no motivation from Exhibit Ko 2 of the trial decision.

The written request for trial argues that Exhibit Ko 16 describes the compound of Working Example 23 of Exhibit Ko 2 as compound 2i having a pyrimidine ring skeleton. Compound 2i of Exhibit Ko 16 is not a compound having a pyrimidine ring skeleton, and thus is not the compound of Working Example 23 of Exhibit Ko 2. Therefore, the description of the written request for trial is incorrect, and the above argument has not been subjected to the trial examination of the trial.

b The written request for trial argues that the Invention does not involve an inventive step by the combination of Exhibit Ko 1 and Ko 2 (Exhibit Ko 79). The above argument of No. 5, 1(1)B is intended to negate the inventive step of the Invention by combining Exhibit Ko 1 with Exhibit Ko 2 and Ko 16, which corresponds to the change of the gist of the statement of the demand. Therefore, it is not permitted.

(B) Even if the aforesaid argument of No. 5, 1(1)B should be approved, the argument by Plaintiffs is not reasonable as in the following items a and b.

In addition, the trial decision stated that it cannot be said that Exhibit Ko 2 "describes a compound where 'R^4' and 'R^5' are 'methyl' and 'methylsulfonyl (SO_2CH_3)' for '$-NR^4R^5$' so as to be technically supported," and "... $-NR^4R^5$ is described as one of a great number of alternatives for 'R^3', and none of these compounds is described in the working examples, nor are the manufacturing method and pharmacological activity described. Therefore, on the basis of the description of Exhibit Ko 2 having no

technical support, ..." The trial decision does not mention that "the compound of the general formula (I) has no technical support."

a(a) The Invention is not X in the following drawing, but R^1-X(R^1: lower alkyl) is a substituent group at the 2-position, and corresponds to -NR^4R^5 of the Exhibit Ko 2 Invention. In the Invention, X is an imino group substituted with an alkylsulfonyl group, whereas in the Exhibit Ko 1 Invention it is an imino group substituted with a methyl group.

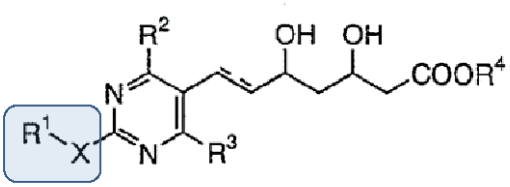


Exhibit Ko 2 lists a great number of alternatives for R^1, R^2, and R^3 in the compounds of general formula (I). There are at least 21.2 million species for a substituent group listed for R^3 of "particularly preferable compound" (Exhibit Ko 80). "Particularly extremely preferable compound" includes methyl, isopropyl, tert-butyl and substituted or non-substituted phenyl for substituent group (R^3) at the 2-position of the pyrimidine ring, all of which are the groups with no hydrophilicity, not including -NR^4R^5.

Further, in NR^4R^5 of Exhibit Ko 2, R^4 and R^5 may be the same or different from each other, and "particularly preferable compound" is "methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, phenyl, benzyl, acetyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl or phenylsulfonyl." Furthermore, none of the specific examples of NR^4R^5 is disclosed. In Working Examples, the substituent group at the 2-position of the pyrimidine ring is methyl (Working Example 8) and phenyl (Working Example 23). A compound with -NR^4R^5 is not disclosed.

As seen above, Exhibit Ko 2 lacks any specific description of even a compound having -NR^4R^5, let alone a compound having -$N(CH_3)(SO_2CH_3)$ at the 2-position of the pyrimidine ring. Therefore, there is no motivation to focus on -NR^4R^5, which is not included in "particularly extremely preferable compound" of R^3, and further intentionally select a methyl group and a methylsulfonyl group for R^4 or R^5 of -NR^4R^5 from numerous substituent groups.

(b) According to the argument by Plaintiffs, a person ordinarily skilled in the art would recognize that the compound manufactured by a manufacture working

example other than Working Examples 8, 15, and 23 of Exhibit Ko 2 might not exhibit the HMG-CoA reductase inhibiting activity. All the statins manufactured by Working Examples 8, 15, and 23 are compounds having a methyl or phenyl (lipophilic substituent group) at the 2-position of the pyrimidine ring.

Therefore, according to the argument by Plaintiffs, a person ordinarily skilled in the art should construe the compounds specifically disclosed as an active compound; i.e., a compound having a methyl or phenyl as a substituent group R^3 at the 2-position of the pyrimidine ring, as meaning the best mode of the invention disclosed in Exhibit Ko 2, and would not be motivated to select $-NR^4R^5$ as R^3, for which none of specific compounds is disclosed.

b(a) The description of "manufacturing method of the compound of the general formula (I)" of Exhibit Ko 2 that Plaintiffs pointed out relates to a method of producing a compound where "phenyl (C_6H_5)" is selected as "R^3," and does not relate to a method for producing a compound where "$-NR^4R^5$" is selected as "R^3."

Furthermore, there was common general technical knowledge as of the priority date that a method for producing a compound with a phenyl for "R^3" was applicable to the whole range of the compound of general formula (I).

Therefore, it cannot be said that a person ordinarily skilled in the art could understand the method for synthesizing a compound where "$-NR^4R^5$" is selected as "R^3" from the description of the manufacturing method as Plaintiffs pointed out.

(b) The difficulty in predicting the pharmacological activity of a compound from only a structure of the compound was a matter of common general technical knowledge as of the priority date.

Exhibit Ko 2 fails to disclose any specific data for HMG-CoA reductase inhibiting activity, and thus a person ordinarily skilled in the art could not understand that the compound of general formula (I) of Exhibit Ko 2 exhibits an HMG-CoA reductase inhibiting activity.

Furthermore, as in the aforesaid item a(b), a person ordinarily skilled in the art would recognize that the compounds manufactured in the manufacture working examples other than Working Examples 8, 15, and 23 of Exhibit Ko 2 might not exhibit HMG-CoA reductase inhibiting activity, and thus would understand that the description of "The active compounds of Working Examples 1 to 23 showed higher activity compared to Mevinolin." of Working Example 24 of Exhibit Ko 2 was incorrect.

(c) The compounds 2r to 2w of Exhibit Ko 16 lack "-NR^4R^5" for "R^3." Thus it cannot be said that there is a technical support for the case where "-NR^4R^5" is selected as "R^3."

(d) Plaintiffs argue that "one can find technical support of HMG-CoA reductase inhibiting activity for the compounds of general formula (I) of Exhibit Ko 2," since Exhibit Ko 16, and Ko 73 to Ko 75 disclosed before the priority date that "a compound with a very similar structure" to the compounds of Working Examples 8 and 23 of Exhibit Ko 2 had a HMG-CoA reductase inhibiting activity. However, it is not permissible to argue as if the inhibiting activity of a compound with a different structure might apply to the compound of Working Examples of Exhibit Ko 2 by use of ambiguous language such as "a compound with a very similar structure."

(C) European Patent Application No. 330057 (Exhibit Otsu 10) corresponding to Exhibit Ko 2 had already been withdrawn before the priority date (Exhibit Otsu 6); however, if Bayer intended to continue the development of the compound disclosed in Exhibit Ko 2, Bayer could aim to obtain a patent for this application as a matter of course.

Consequently, the fact of the withdrawal of the application shows that Bayer ceased to develop the compound disclosed in Exhibit Ko 2; i.e., Bayer determined that it was not promising for an HMG-CoA reductase inhibitor.

So long as such circumstances were known before the priority date, a person ordinarily skilled in the art would naturally avoid a compound that Bayer determined to be not promising. Also from this viewpoint, a person ordinarily skilled in the art would not select the substituent group disclosed in Exhibit Ko 2.

(D) The trial decision mentioned that "the compound of formula I is 'prima facie' expected to have an HMG-CoA reductase inhibiting activity." This description means that, if a person ordinarily skilled in the art who reads Exhibit Ko 1 should modify the Exhibit Ko 1 Invention, the candidate would fall within the scope of formula I. Similarly, if one selects a substituent group at the 2-position of the pyrimidine ring from Exhibit Ko 2, the candidate falls within the range of R^3. However, R^3 extends to a large number of substituent groups. In order to overcome the difference (1-i), -NR^4R^5 (R^4: methyl, R^5: methylsulfonyl) should be selected from them.

Exhibit Ko 2 lists a large number of functional groups for R^3. To select the functional group making a difference (-NR^4R^5, R^4: lower alkyl, R^5: alkylsulfonyl) from these functional groups and combine with the Exhibit Ko 1 Invention, some suggestion or motivation of the combination is necessary. Even if a person ordinarily skilled in the art should try to increase hydrophilicity of the compound of the Exhibit Ko 1 Invention, a person ordinarily skilled in the art could not select the functional group making the above difference only on the basis of the generalized property of hydrophilicity.

There is no suggestion or motivation in Exhibit Ko 2 for a person ordinarily skilled in the art to select particularly -NR^4R^5 from R^3, and a functional group making the above difference therefrom, and combine with Exhibit Ko 1 Invention.

(E) Therefore, there is no motivation to replace "dimethylamino group" of the Exhibit Ko 1 Invention with "-$N(CH_3)(SO_2CH_3)$" on the basis of the description of Exhibit Ko 2.

C Motivation from the common general technical knowledge

(A)a As in the following, there was no motivation to modify the Exhibit Ko 1 Invention or increase hydrophilicity.

(a) Five companies who had started the research and development of a statin with a pyrimidine skeleton ceased by the priority date. Therefore, it was well-known as of the priority date that a statin with a pyrimidine skeleton was not promising for an HMG-CoA reductase inhibitor.

Therefore, a person ordinarily skilled in the art who tried to develop an excellent HMG-CoA reductase inhibitor would not be motivated to modify the Exhibit Ko 1 Invention of a statin with a pyrimidine skeleton.

(b) The Invention and the Exhibit Ko 1 Invention both relate to a pharmaceutical product to be administered for chronic diseases such as hypercholesteremia and hyperlipidemia. It was a matter of common general technical knowledge as of the priority date that a dose period of the pharmaceutical product was longer than that of other pharmaceutical products, and thus low toxicity was strongly desired (Exhibit Otsu 20).

Therefore, if a person ordinarily skilled in the art should intend to modify the compound of the Exhibit Ko 1 Invention, he would first confirm the toxicity as a matter of course. If toxicity of the compound of the Exhibit Ko 1 Invention is found,

he should stop the modification.

Further, the compound of the Exhibit Ko 1 Invention is omitted from the candidates for development of Sandoz due to the problem of liver toxicity (Exhibit Otsu 21). Therefore, a person ordinarily skilled in the art would not intend to develop a new HMG-CoA reductase inhibitor by modifying the compound of the Exhibit Ko 1 Invention (Exhibit Otsu 4).

(c) As in the aforesaid A(C), it was known as of the priority date that liver selectivity did not necessarily have a correlation with hydrophilicity, and it was well-known that the hydrophilicity of statin did not have a correlation with HMG-CoA reductase inhibiting activity. Therefore, a person ordinarily skilled in the art would not conceive that excellent HMG-CoA reductase inhibiting activity may be achieved by improving the hydrophilicity of a statin.

b Even if there were a motivation to improve hydrophilicity of an HMG-CoA reductase inhibitor, there was no motivation to improve hydrophilicity with the fixed substituent group of methyl at the 2-position of the pyrimidine ring as set forth below.

(a) Exhibit Ko 1 itself discloses that a compound with increased hydrophilicity through the introduction of a substituent group other than p-fluorophenyl at the 4-position of the pyrimidine ring was manufactured in Working Example 11d as "a preferable compound," and its excellent inhibiting activity was confirmed.

A person ordinarily skilled in the art who intended to modify the compound of the Exhibit Ko 1 Invention would always refer to the disclosure of Exhibit Ko 1, and thus would naturally try to introduce a hydrophilic substituent group at the 4-position of the pyrimidine ring, not at the 2-position.

(b) There was no common general technical knowledge as of the priority date that the introduction of a dihydroxyheptenoic acid structure at the 5-position, a p-fluorophenyl group at the 4-position, and an isopropyl group at the 6-position in a pyrimidine skeleton statin resulted in excellent HMG-CoA reductase inhibiting activity.

As of the priority date, there were numerous statins with different substituent groups at the positions corresponding to the 4- and 6-positions of the pyrimidine ring, including Pitavastatin, BMY21950, BMY22089, and HR780.

Exhibit Ko 1 and Ko 2 disclose a combination other than a combination of a

parafluorophenyl group at the 4-position and an isopropyl group at the 6-position as a compound with a pyrimidine ring skeleton that might have HMG-CoA reductase inhibiting activity.

Two cases out of three cases where HMG-CoA reductase inhibiting activity may be demonstrated in the compounds synthesized by the manufacture working examples 1 to 23 of Exhibit Ko 2 have a methyl group at the 6-position, not an isopropyl group (Working Examples 8 and 15).

Further, Exhibit Ko 26, Ko 27, and Ko 76 are not documents of a statin compound containing a pyrimidine ring. There is no description that, "regarding a p-fluorophenyl group at the 4-position of the pyrimidine ring and an isopropyl group at the 6-position of the pyrimidine ring," "these combinations have a strong activity."

Therefore, a person ordinarily skilled in the art would not necessarily fix a p-fluorophenyl group at the 4-position and an isopropyl group at the 6-position in modifying the compound of the Exhibit Ko 1 Invention, nor focus only on the substituent group at the 2-position of the pyrimidine ring.

If a person ordinarily skilled in the art tries to modify the Exhibit Ko 1 Invention with reference to Exhibit Ko 1, the range should fall within a range of general formula I of Exhibit Ko 1.

Exhibit Ko 1 describes a C_{1-6} alkyl, C_{1-6} cycloalkyl, $(CH_2)_m$-substituted or non-substituted phenyl, benzyloxy, benzylthio, and disubstituted amino group as substituent groups at the 2-position of the pyrimidine ring in the compound of general formula I (Claim 1). In Working Examples, in addition to a disubstituted amino group such as $-N(CH_3)_2$, there used were a phenyl (Working Examples 3 to 8), an isopropyl (Working Examples 9, 11a and 10f), a tert-butyl group (Working Examples 10a, 11b, 11e, and 11g), and a methyl (Working Examples 10b, 10e, 10h, 11c, 11f, and 11i) for a substituent group at the 2-position.

Therefore, a person ordinarily skilled in the art who read Exhibit Ko 1 should understand that the substituent group at the 2-position of the pyrimidine ring was not necessarily fixed, but might be the above substituent group.

To change the Exhibit Ko 1 Invention into the Invention, it should undergo the following steps: [i] Fix nitrogen atom binding to the 2-position of the pyrimidine ring and two methyl groups binding to the nitrogen atom of the Exhibit Ko 1 Invention; [ii] Fix one nitrogen-methyl group bond, insert the other functional group between another nitrogen-methyl group bond; and [iii] Focus on NR^4R^5 suitable for the purpose of [ii] among R^3 of Exhibit Ko 2 and further specify R^5 as an alkylsulfonyl group. This process may not be implemented without a priori recognition of the Invention.

Even if a person ordinarily skilled in the art should try to improve hydrophilicity, he could modify a methyl group (e.g. -CH_2OH), or substitute a methyl group with the other group. Thus there is no certainty to fix the methyl group.

In pyrimidine skeleton statins that a person ordinarily skilled in the art actually manufactured and tested by the priority date, almost all the statins introduced a lipophilic group at the 2-position (Exhibit Ko 1, Ko 2, Ko 80, Otsu 5, Otsu 28, and Otsu 29). Therefore, also from this viewpoint, there was no motivation to select the 2-position for the improvement of hydrophilicity.

c As set forth below, there was a disincentive to introduce a methylsulfonyl group at the 2-position of pyrimidine ring as of the priority date (Exhibit Ko 80 and Otsu 4).

(a) Exhibit Ko 16 discloses that a substituent group at the 2-position of the pyrimidine ring is the most important for biological activity such as HMG-CoA reductase inhibiting activity, and furthermore the activity may be significantly increased by rendering the substituent group at the same position lipophilic, and the substituent group at the same moiety may be assumed to become an additional anchor by interacting with the hydrophobic region of an enzyme to strengthen the bonding, and the lipophilic substituent group specifically includes an alkyl group and a phenyl group.

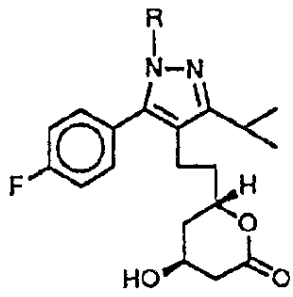
On the contrary, a person ordinarily skilled in the art would naturally expect that the increased hydrophilicity of the substituent group at the 2-position would result in the decrease of HMG-CoA reductase inhibiting activity. Even if a person ordinarily skilled in the art should try to increase hydrophilicity of the compound of the Exhibit Ko 1 Invention, he would not try to introduce a highly hydrophilic substituent group at the 2-position, which would compromise the most important factor of the enzyme inhibiting activity for an HMG-CoA reductase inhibitor, but would naturally introduce the substituent group at a position other than the 2-position.

Since hydrophilicity and lipophilicity are relative indicators, it was a matter of common knowledge for a ordinarily person skilled in the art as of the priority date to understand that if "higher lipophilicity results in a significant increase of inhibiting activity," then "the shift to hydrophilicity results in a significant decrease of activity."

In addition, Plaintiffs argue that the order of ClogP for various compounds of Exhibit Ko 16 does not necessarily coincide with the order of relative (CSI) efficacy (HMG-CoA reductase inhibiting activity), but these compounds are not arranged at an equal interval for ClogP. When a number of compounds are distributed in a narrow

range of ClogP, the order of relative (CSI) efficacy tends to be changed. Therefore, comparing the order of ClogP and the order of relative (CSI) efficacy, no accurate findings may be obtained with respect to the correlation between ClogP and relative (CSI) efficacy.

(b) As of the priority date, a sulfonamide structure was an extremely rare substituent group among statin-based compounds (Exhibit Otsu 18). The only compound with a lactone structure specific to a statin-based compound or a free acid structure thereof is compound No. 27 of Exhibit Ko 76 (Exhibit Otsu 17) in the following drawing. The biological activity of the compound is less than 10% compared to a compound without a sulfonyl group (No. 26; R=tolyl group (4-methylphenyl group)). The introduction of a sulfonyl group into compound No. 26 resulted in a decrease of HMG-CoA reductase inhibiting activity to a factor of about one-eleventh.



(R=4-tolylsulfonyl group)

Even if there was a motivation to improve hydrophilicity of the Exhibit Ko 1 Invention, a person ordinarily skilled in the art would naturally avoid the introduction of a methylsulfonyl group at the 2-position of the compound of the Exhibit Ko 1 Invention.

d Exhibit Ko 16 recommends a bulky, lipophilic substituent group (including an alkyl group) for the substituent group at the 2-position of the pyrimidine ring (R^3 in Exhibit Ko 16), not a hydrophilic substituent group.

Therefore, a person ordinarily skilled in the art should focus on a lipophilic alkyl group, in particular, bulky groups such as isopropyl, tert-butyl, and phenyl, although he would consider Exhibit Ko 16 in addition to Exhibit Ko 1 and Ko 2.

(B) Even if it is a common general technical knowledge to change the compound by stages, in the modification of a lead compound, the research is

conducted to replace a substituent group with another substituent group with similarities in size or electronic properties so as not to drastically change a size of the substituent group or electronic properties of the substituent group of the compound of the Exhibit Ko 1 Invention (Exhibit Otsu 67). Therefore, the introduction of an electron-withdrawing, high polarity group (Exhibit Ko 56) of a methylsulfonyl group that has a great impact on steric structure with electronic properties largely different from those of a methyl group does not change the structure of compound by stages, nor is it a modification that avoids changing a size of the substituent group. There is no motivation for a person ordinarily skilled in the art to select this. On the contrary, a person ordinarily skilled in the art should avoid selecting the substituent group.

(C) The inhibiting activity of cholesterol biosynthesis (ED_{50}) and HMG-CoA reductase inhibiting activity (IC_{50}) are not the same activity, but differ in measurement method. Therefore, it cannot be said that HMG-CoA reductase inhibiting activity would be 125 times that of Compactin even if the inhibiting activity of cholesterol biosynthesis were 125 times.

(D) Since inventive step and the support requirement are different patent requirements, it cannot be a ground for rescission of the JPO decision that the determination criteria are different from each other. Therefore, the argument by Plaintiffs is incorrect on its premise.

(3) Errors in the determination of the effect of the Invention

A With regard to the invalidation reason 1 of the trial, the specific compound of Working Example 1b) of Exhibit Ko 1 is the primarily cited invention (Exhibit Ko 1 Invention) (Exhibit Ko 79, Otsu 67 etc.), whereas the argument by Plaintiffs is intended to negate the inventive step of the more specific concept of Invention 1 with a criterion of selection invention on the premise that the above concept of the compound of general formula (I) of Exhibit Ko 2 be a primarily cited invention. This corresponds to the substitution of the primarily cited invention.

The trial decision finds the Exhibit Ko 1 Invention to be the invention of a specific compound in accordance with Plaintiff X's argument. Therefore, no room is left for argument about the selection invention in invalidation reason 1 argued by Plaintiffs.

In the trial of the case, such argument is not presented. It is not a subject of trial examination as a matter of course. It is not permitted for Plaintiffs to argue in

this manner in this lawsuit.

First of all, the compound of Exhibit Ko 1 Invention is not a selection invention of general formula (I) of Exhibit Ko 2.

B(A)a(a) From the test results of HMG-CoA reductase inhibiting activity described in Exhibit Ko 3 and Ko 5, four-times tests show that the compound of the Invention 1 of Rosuvastatin calcium has a two-time to nine-time higher activity compared to the compound of the Exhibit Ko 1 Invention.

Therefore, it is recognized that there are at least two times or more of significant difference in activity between Invention 1 and the Exhibit Ko 1 Invention even in view of the test errors (Exhibit Ko 64, Otsu 4. 3.2 times for Exhibit Ko 64). Given that the compound of Exhibit Ko 1 Invention is a standard for comparison, it has a superior HMG-CoA reductase inhibiting activity compared to the compound of the Exhibit Ko 1 Invention.

(b) The compound of the Exhibit Ko 1 Invention has high liver toxicity (Exhibit Otsu 21 to Otsu 27), whereas the compound of Invention 1 of Rosuvastatin calcium has low toxicity (Exhibit Otsu 42).

It was a matter of common general technical knowledge as of the priority date that higher liver selectivity might accordingly result in higher load on the liver, and might possibly increase liver toxicity. According to the argument by Plaintiffs, Rosuvastatin calcium has a higher hydrophilicity compared to the compound of the Exhibit Ko 1 Invention, and thus has high liver selectivity, and is thus expected to impose a heavy load on the liver. Nevertheless, the liver toxicity of Rosuvastatin calcium is much lower than that of the compound of the Exhibit Ko 1 Invention.

(c) Rosuvastatin calcium is expected to show a comparable effect with a dose amount in a living body one-half or less that of the compound of the Exhibit Ko 1 Invention, and thus has a further broader range of safety dose.

Such excellent effect of low toxicity of Invention 1 is a particularly significant effect that goes beyond the scope predictable from the Exhibit Ko 1 Invention in view of the state of the art as of the priority date.

b Further, it was known as of the priority date that the introduction of a hydrophilic substituent group at the 2-position of the pyrimidine ring of a statin or the introduction of a sulfonamide structure into a statin resulted in a significant decrease of

HMG-CoA reductase inhibiting activity (Exhibit Ko 16, Otsu 17). Therefore, a person ordinarily skilled in the art would expect that HMG-CoA reductase inhibiting activity would be decreased if one methyl group of a dimethylamino group at the 2-position of the pyrimidine ring of the Exhibit Ko 1 Invention should be substituted with a more hydrophilic sulfonyl group to form a sulfonamide structure.

c Consequently, it cannot completely be expected from the Exhibit Ko 1 Invention or common general technical knowledge that Rosuvastatin calcium has an inhibiting activity at least two times higher than that of the compound of the Exhibit Ko 1 Invention.

(B) The effect of the Invention may be evaluated by comparing with sodium Mevinolin that had been known as an HMG-CoA reductase inhibitor, once the difficulty of the structure should be affirmed. What is used for a positive control is a compound whose effectiveness has already been confirmed. If it is not inferior to the positive control, the effectiveness of the test compound may be demonstrated. This is a matter of common general technical knowledge for a person ordinarily skilled in the art. It does not necessarily have a higher HMG-CoA reductase inhibiting activity compared to the Exhibit Ko 1 Invention, nor is the compound of the Exhibit Ko 1 Invention the only comparative control.

(C) HMG-CoA reductase inhibiting activity is a property different from cell permeability. Even if increasing the hydrophilicity of compound may result in the decrease of permeability into non-hepatic cells (and as a result, increase the selectivity of liver cell with regard to permeability), the effect on HMG-CoA reductase inhibiting activity is not predictable.

For the purpose of increasing hydrophilicity of a compound, various substituent groups may be used. In addition, a person ordinarily skilled in the art may find many parts to be substituted with another group for the purpose of increasing the hydrophilicity of a compound in the compound. Therefore, there are many alternatives to increase hydrophilicity. When the 2-position of the pyrimidine ring of the Exhibit Ko 1 Invention among the alternatives was substituted with -$N(CH_3)(SO_2CH_3)$, the HMG-CoA reductase inhibiting activity was improved, which was unexpected.

Consequently, if the compound of Invention 1 should have an inhibiting activity comparable to the Exhibit Ko 1 Invention, it is just a particularly significant effect that

goes beyond the scope predictable from the Exhibit Ko 1 Invention in view of the state of the art as of the priority date. Even only with this fact, the inventive step would be affirmed.

A compound with an HMG-CoA reductase inhibiting activity comparable to that of the conventional HMG-CoA reductase inhibitors may contribute to the improvement of the industry from a viewpoint of increasing the alternatives of new HMG-CoA reductase inhibitors.

(D) Rosuvastatin calcium of the compound according to Invention 1 has a very strong HMG-CoA reductase inhibiting activity compared to the existing HMG-CoA reductase inhibitors (Fluvastatin, Simvastatin, Pravastatin, Cerivastatin, and Atorvastatin) (Exhibit Otsu 34 to Otsu 36).

Rosuvastatin calcium realizes a lower level of LDL-C (Low Density Lipoprotein Cholesterol) in a wide range of doses as compared to the other approved statins (specifically, Atorvastatin, Simvastatin, and Pravastatin).

Furthermore, the existing statin-based HMG-CoA reductase inhibitors could not control LDL-C to a targeted value for many patients (in particular high-risk patients) (Exhibit Hei 10). Rosuvastatin calcium provided great therapeutic effects for these patients.

As seen above, the HMG-CoA reductase inhibiting activity of Rosuvastatin calcium has a clinically significantly important value.

This is also a particularly significant effect that goes beyond the scope expected from the Exhibit Ko 1 Invention in view of the state of the art as of the priority date.

C(A) Rat liver microsome method was commonly used as of the priority date as the standard method to measure in vitro inhibiting activity of HMG-CoA reductase inhibitors (Exhibit Ko 1, Ko 2, Ko 7, Ko 8, Ko 15, Ko 16, Ko 19, Ko 26, Ko 27, and Ko 64). Even if absolute value of activity of the test compound might sometimes vary between different measurement trials, it was common general technical knowledge as of the priority date that this method allowed us to clearly show a relative relationship of inhibiting activity between test compounds in the same measurement trial.

Further, it was common general technical knowledge as of the priority date that, when the HMG-CoA reductase inhibiting activity is measured by rat liver microsome method, IC_{50} was used as an indicator of "inhibiting activity" (Exhibit Ko 1, Ko 2, Ko 7, Ko 8, Ko 15, Ko 16, Ko 19, Ko 26, and Ko 27).

The description details an experimental method by use of liver microsome fraction ([0040], [0041]). A person ordinarily skilled in the art would thus naturally understand that "IC_{50}" was an indicator of "inhibiting activity," and the numerical values of Table 4 showed a relative activity of each compound, given that the inhibiting activity of Mevinolin assessed by IC_{50} is 100, from the description in paragraph [0041] of "The activities of the compounds of the Invention are shown in Table 4 as comparative data, based on the assumption that the activity of Mevinolin (sodium salt) as the reference drug is 100."

(B) Table 4 discloses that the inhibiting activity of the test compound Ia-1 (sodium salt of the compound according to the Invention 1) was "442," given that the inhibiting activity of sodium salt of Mevinolin is "100." Therefore, a person ordinarily skilled in the art would instantly recognize that Mevinolin sodium salt and test compound Ia-1 were measured under the same conditions, and a result of the inhibiting activity of the test compound Ia-1 being higher than that of Mevinolin sodium salt was obtained.

Further, Table 4 describes at the bottom that "As seen above, it is believed that particularly the compounds of the present invention exhibit HMG-CoA reductase inhibition activities superior to that of Mevinolin." ([0042]). A person ordinarily skilled in the art could recognize from this description that the result of Table 4 exhibits a stronger HMG-CoA reductase inhibiting activity of the test compound Ia-1 as compared to Mevinolin.

Therefore, a person ordinarily skilled in the art could understand the meaning of the numerical values of Table 4, and deduce from the result that the compound of the Invention 1 had a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin.

D(A) It is evident from the result of Exhibit Ko 3 that the compound of Invention 1 has a higher HMG-CoA reductase inhibiting activity as compared to sodium Mevinolin.

Exhibit Ko 3 describes an experimental result of HMG-CoA reductase inhibiting activity conducted after the filing. In Exhibit Ko 3, the compound of the Invention 1 had a HMG-CoA reductase inhibiting activity about two times higher than that of the compound of the Exhibit Ko 1 Invention.

The activity is objectively determined without relation to the prosecution history. The description describes the relative activity of sodium Rosuvastatin

(Sodium Mevinolin is a standard for comparison) as well as the assessment method. It is naturally acceptable to make an additional comparison with a publicly known compound other than sodium Mevinolin by a method for assessment similar to that cited in the description.

(B) The Patentee has never argued in the examination process that "about 2 times" is not a significant effect. The Exhibit Ko 2 Invention was not cited as a reference in the notice of reasons of refusal (Exhibit Ko 71). Therefore, the Patentee did not have to argue in the written opinion about the effect as a selection invention in order to establish the inventive step over the Exhibit Ko 2 Invention.

Therefore, the argument by Plaintiffs that "the standard for comparison of Invention 1 is the Exhibit Ko 1 Invention, and Invention 1 cannot be seen as having significant effects unless the Invention is about 9 times stronger in HMG-CoA reductase inhibiting activity" is incorrect on its premise.

E(A) The compound according to Invention 1 of Rosuvastatin calcium has a very strong inhibiting activity of cholesterols biosynthesis as compared to the existing HMG-CoA reductase inhibitors and also has a long sustained time of synthesis inhibitory effect (Exhibit Otsu 34 to Otsu 36).

Rosuvastatin calcium has strong effects of increasing HDL cholesterol and decreasing triglycerides, and exhibits excellent improvement on clinical state of atherosclerosis, and is thus clinically superior to the other statin-based HMG-CoA reductase inhibitors (Exhibit Otsu 35 to Otsu 41).

(B) Both the Invention and the Exhibit Ko 1 Invention have a longer administration period than the other pharmaceutical products, and thus a poor result of pharmacokinetics makes their clinical use difficult.

Rosuvastatin calcium provided extremely excellent results compared to the compound of Exhibit Ko 1 Invention in the non-clinical Pharmacokinetic Studies for the assessment of disposition (Exhibit Otsu 45 and Otsu 46).

a Cytochrome P450 (CYP) enzyme is composed of various molecular species that differ in substrate specificity, and was well known as a primary drug metabolic enzyme as of the priority date (Exhibit Otsu 47).

The inhibition of the activity of any CYP molecular species by one drug results in the delayed metabolism of other drug(s) that may become a substrate of the CYP

molecular species (i.e. decomposition by the CYP molecular species). Therefore, it was a matter of common general technical knowledge as of the priority date that a drug with a low inhibiting activity against various CYP molecular species was desirable.

Defendant measured the inhibiting activity for Rosuvastatin calcium and the compound of the Exhibit Ko 1 Invention against various CYP enzymes that were well known as of the priority date. Thus the compound of the Exhibit Ko 1 Invention showed a very strong CYP2C9 inhibiting activity as compared to Rosuvastatin calcium (Exhibit Otsu 45).

b It is confirmed by a comparative test that Rosuvastatin calcium has a very high level of metabolic stability as compared to the compound of the Exhibit Ko 1 Invention (Exhibit Otsu 46).

The stability against oxidative metabolism of Rosuvastatin calcium and the compound of Exhibit Ko 1 Invention was measured in human liver cells microsome. The results show that the stability of Rosuvastatin calcium is very high (100%), and the kinetic profiles (in particular sustainability) in human are expected to be good.

On the contrary, the compound of the Exhibit Ko 1 Invention has a fairly low stability (69%), and the kinetic profiles (in particular sustainability) are expected to be poor, which poses a problem in maintaining the effective blood level important for pharmaceutical products. A person ordinarily skilled in the art would conceive that the compound of the Exhibit Ko 1 Invention has a great barrier in proceeding with development (Exhibit Otsu 46).

F As aforementioned, the compound according to Invention 1 of Rosuvastatin compound causes excellent HMG-CoA reductase inhibiting activity unexpected from the Exhibit Ko 1 Invention or the common general technical knowledge, and exhibits high inhibiting activity of cholesterol synthesis as well as excellent clinical effects.

Furthermore, the compound according to Invention 1 of Rosuvastatin compound has low liver toxicity and excellent pharmacokinetics compared to the compound of the Exhibit Ko 1 Invention. Such effects are particularly significant effects that go beyond the scope predictable from the Exhibit Ko 1 Invention in view of the state of art as of the priority date.

It is very difficult to develop a drug for the treatment of hypercholesterolemia with an effective and low toxic pyrimidine skeleton statin (Exhibit Otsu 48 to Otsu 50). Further, the other pharmaceutical companies did not regard pyrimidine skeleton statins as promising. Regardless of these factors, Rosuvastatin calcium according to

Invention 1 has achieved worldwide revenue as a drug for the treatment of hypercholesterolemia (Exhibit Otsu 51 to Otsu 55), and the other pharmaceutical companies are developing analogous compounds (Exhibit Otsu 48). Furthermore, in two lawsuits in the United States, the inventive step of the invention similar to Invention 1 has been affirmed (Exhibit Otsu 8 and Otsu 9).

These facts support the inventive step of Invention 1.

2 Ground 2 for rescission

(1) In the test example of the specification, the evaluation result of HMG-CoA reductase inhibiting activity by use of liver microsome is described for sodium salt of Rosuvastatin, and for sodium salt of Mevinolin as a comparative control.

The compound of formula (I) of Invention 1 corresponds to a statin. Statins have common features of dihydroxyheptenoic acid (or dihydroxyheptanoic acid) or a derivative thereof ("HMG-like moiety") and a skeleton binding to the HMG-like moiety. In an active type circulating plasma, HMG-like moiety is in the form of opened-ring dihydroxyheptanoic acid (or dihydroxyheptenoic acid) (Exhibit Ko 7 and Ko 8).

When a statin compound is administered to a human body, the compound is dissolved into aqueous media in the body. For example, when a statin compound is orally administered, the compound is dissolved into a gastrointestinal fluid. In the dissolution process, the statin compound forms a cation (e.g. sodium cation and calcium cation) and an anion (e.g. Rosuvastatin anion) according to the original structure. Once a statin compound is dissolved, a statin anion freely interacts with the other ions present in a gastrointestinal fluid. Gastrointestinal fluid includes a number of ions, such as hydrogen, sodium, potassium, and magnesium cations. Therefore, Rosuvastatin anion may associate with all these cations to be liberated. After dissolution into gastrointestinal fluid, Rosuvastatin anion penetrates into the blood system by passing through the intestinal tract. In the blood system, Rosuvastatin anion may associate with all the cations (sodium is domestic) in the blood system to be liberated.

As aforementioned, it is no longer possible to find what kind of salt Rosuvastatin anion was derived from (Exhibit Hei 13).

Therefore, the recitation of the scope of claims is supported by the test examples of the description.

(2) Problem to be solved by the Invention

A(A) An active ingredient of a pharmaceutical product requires pharmacological activity to the extent that it may become a pharmaceutical product. Even if the pharmacological activity of a new active ingredient is at the same level as that of an active ingredient that has been commercially available, the new active ingredient has a technical value in that it provides an alternative means for solution.

For example, if two active ingredients show a similar level of pharmacological activity, this might cause a difference between patient groups to be administered from another viewpoint (e.g. difference in pharmacokinetics and adverse events). In this case, two active ingredients both have technical value.

Therefore, a pharmacological activity beyond that of all the conventional active ingredients is not required as a problem of the support requirement.

(B) If the argument by Plaintiffs is correct, the inventor is obliged to conduct comparative tests with any and all of the publicly known compounds for the claimed compounds of an invention and establish its superior activity compared to the publicly known compounds. Such conclusion is not reasonable.

B(A) The compounds of Inventions 1, 2, 5, and 9 to 11 are encompassed into the compound represented by the general formula (I) described in paragraph [0004] of the description. Therefore, the problem to be solved by Inventions 1, 2, 5, and 9 to 11 lies in the provision of a compound having an excellent HMG-CoA reductase inhibiting activity, and the problem to be solved by Invention 12 lies in the provision of an HMG-CoA reductase inhibitor including such a compound. This can be seen from the description in paragraphs [0003] and [0004] of the description.

Further, it can be seen from the description of paragraph [0003] that the degree of the HMG-CoA reductase inhibiting activity is sufficient if it is the extent that the compound may become a pharmaceutical product "for suppressing the synthesis of cholesterols."

Consequently, the objective of the Invention is to provide an excellent HMG-CoA reductase inhibiting compound, or an HMG-CoA reductase inhibitor comprising the compound. The sufficiency of the support requirement should be determined by whether the compounds of Inventions 1, 2, 5, and 9 to 11 may be obtained (may be manufactured) and whether the Detailed Description of the Invention is described to the extent that allows a person ordinarily skilled in the art to recognize that the obtained compound has an excellent HMG-CoA reductase inhibiting activity.

(B) Setting aside this point, Mevinolin is a representative statin-based HMG-CoA reductase inhibitor that was commercially available as of the priority date, and it was a common general technical knowledge as of the priority date to use Mevinolin as a comparative control for the activity assessment of a new statin-based HMG-CoA reductase inhibitor (Exhibit Ko 1, Ko 2, Ko 7, Ko 15, Ko 19, Ko 27, etc.).

(C) The argument by Plaintiffs relying on Exhibit Ko 16 compares an absolute value of HMG-CoA reductase inhibiting activity IC_{50} obtained in different experimental systems via Mevinolin, and is thus not reasonable.

Further, in vivo cholesterol biosynthesis inhibiting activity and in vitro HMG-CoA reductase inhibiting activity are not the same activity, and the measurement method is different. The argument by Plaintiffs tries to apply an activity ratio obtained with respect to one activity to a different activity, and is thus not reasonable.

C The problem to be solved by the invention should be formulated on the basis of the content of the description in view of the common general technical knowledge as of the filing, and the prosecution history should not be considered. Thus it is not affected by the subjective view of the patent applicant.

(3) The fact that a person ordinarily skilled in the art could recognize that the problem to be solved by Invention 1 might be solved

A The description discloses in paragraphs [0040] to [0042] that the compound of (Ia-1), a sodium salt of Rosuvastatin calcium according to Invention 1, has a HMG-CoA reductase inhibiting effect of a relative activity of 442 with the inhibiting activity of sodium Mevinolin given as 100. A person ordinarily skilled in the art could recognize that the compound Ia-1 (sodium salt) shows a similar activity to its calcium salt in a living body. Therefore, the specification discloses that Invention 1 has a strong HMG-CoA reductase inhibiting activity as compared to sodium Mevinolin.

Furthermore, Exhibit Ko 3 actually shows that its calcium salt of Rosuvastatin calcium has a higher HMG-CoA reductase inhibiting activity as compared to sodium Mevinolin, which supports that the above deduction is correct.

B Defendant definitely argues in the written statement dated March 24, 2016 for trial that Invention 1 is supported by data of compound Ia-1 of the specification (Exhibit Otsu 69).

First of all, the prosecution history should not be considered in considering

"whether or not the inventions recited in the Claims might fall within the scope, in which a person ordinarily skilled in the art could recognize that the object of the invention might be solved by the description of the Detailed Description of the Invention, or in view of common general technical knowledge as of the filing without such description or suggestion." Therefore, it is not affected by the subjective view of the Patentee (Exhibit Otsu 62).

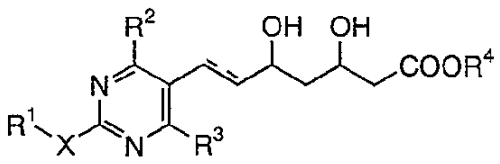
(4) A person ordinarily skilled in the art could understand that the overall range of compounds of Invention 1 have a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin

A In the trial, the argument about the noncompliance of support requirement (invalidation reason 2) only focuses on the point that the calcium salt of compound Ia-1 of the specification is not supported among the compounds of Invention 1. Therefore, it is not permitted to add in the suit against trial decision a new argument to the effect that the overall range of the compound of Invention 1 is not supported.

B Compounds 2r and 2s of Exhibit Ko 16 are different from compounds 2t, 2u, 2v, and 2w not only in a substituent group at the 6-position of the pyrimidine ring (corresponding to R^1 of Exhibit Ko 16), but also in a substituent group at the 2-position (corresponding to R^3 of Exhibit Ko 16). Therefore, the argument by Plaintiffs that emphasizes only the difference in a substituent group at the 6-position is not reasonable.

Rosuvastatin has achieved improved HMG-CoA reductase inhibiting activity by the modification of a substituent group at the 2-position of the pyrimidine ring (-XR^1; R^1 is methyl, X is -$N(SO_2CH_3)$-) in the case of R^2 being parafluorophenyl and R^3 being isopropyl in formula (I).

The following formula (I):



(R^1 is a lower alkyl; R^2 is a phenyl substituted with a halogen; R^3 is a lower alkyl; the dashed line represents the presence or absence of a double bond.)

The improved HMG-CoA reductase inhibiting activity due to the modification of this substituent group at the 2-position may be reasonably expected not only in

Rosuvastatin but also in the other compounds within the above limited scopes of R^2 and R^3.

Therefore, Invention 1 falls within such a scope that allows a person ordinarily skilled in the art to recognize that the objective of the invention may be solved in view of the specification and the common general technical knowledge.

Accordingly, a person ordinarily skilled in the art could understand that the compound of Invention 1 might become a compound showing a comparable HMG-CoA reductase inhibiting activity from the disclosure of the specification that compound Ia-1 had a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin.

(5) As seen above, the Invention conforms to the support requirement.

Further, the argument of ground 2(3) for rescission with respect to Invention 1 presented by Plaintiffs may not apply to Inventions 2 and 11.

No. 7 Judgment of this court

1 Defense prior to the pleading on the merits

(1)A The request for trial was made on March 31, 2015, and thus the Patent Act as of that date (the Patent Act prior to amendment by Act No.36 of 2014) shall be applied to the request for trial. Article 123, paragraph (2) of the Patent Act at that time specified that "a trial for invalidation of a patent may be demanded by anyone (hereinafter omitted)," which means the permission of trial for invalidation of a patent regardless of the presence or absence of proprietary interest. (Additionally, there is a separate provision with regard to a misappropriated application or violation of joint application, but it has nothing to do with this case. Thus no reference is made to this provision. This can apply to the following determination.)

The spirit of such provision is construed such that a patent right is an exclusive right, which prohibits the use of technique according to a patent by anyone without permission of the patentee, and it is an action that becomes beneficial for all the people and it serves the public interest to invalidate an erroneously registered patent, and in view of such nature, a person entitled to demand for invalidation trial of the patent is not limited to a private proprietary interests, but extends to the public.

Further, the trial for invalidation of a patent may be demanded even after the expiration of the life of a patent (Article 123, paragraph (3) of the Patent Act). Therefore, even if the life of a patent is expired, it is obvious that an interest to make a request for an invalidation trial, and thus a legal interest for litigation to rescind a trial

decision that dismissed the request for an invalidation trial, would not diminish.

B Regarding a suit for rescission of a trial decision that dismissed the request for an invalidation trial after the expiration of a life of a patent, Defendant cites a Tokyo High Court judgment made on December 26, 1990 and argues that a legal interest for litigation is affirmed only in the case where there is any substantial legal disadvantage for demandant of the trial due to the existence of the patent right.

However, if the case where a legal interest for litigation to rescind a trial decision that dismissed the request for an invalidation trial of a patent is affirmed after the termination of the patent right is limited to: the case where there is a dispute between the patentee and the demandant for trial such as a claim for compensation for damage that poses a problem as to whether the patent is valid or invalid, or there is any factual relationship that might possibly become a cause developing such dispute in the future even after the expiration of a life of a patent, and there is any substantial legal disadvantage for the demandant of the trial due to the existence of the patent right, a legal interest for litigation is an ex officio search matter, and thus a court should search and determine the presence or the absence of dispute that poses a problem as to whether the patent is valid or invalid, or the presence or the absence of a factual relationship that might possibly become a cause developing such dispute in the future even after the expiration of the life of the patent. Further, for such a goal, a court should request parties concerned to argue about the existence of an actual dispute as to whether or not a product manufactured by himself might be an infringing product of a specific patent, or the existence of a factual relationship that might possibly become a cause developing such dispute in the future. Such argument may include an argument of a fact that might possibly be harmful to himself, including a fact that a product manufactured by himself might have a structure that might be evaluated as an worked product of the patent invention.

It is not reasonable to oblige a party concerned to argue such fact.

C Indeed, if there are special circumstances where the complete loss of possibility of anyone being subjected to a claim for damages or gaining unjust enrichment from, or being imposed criminal penalties for, conduct within the lifetime of patent right and after the expiration of patent right, e.g. the case where 20 years has already passed after the expiration of the life of a patent, it means that no one runs a risk of suffering disadvantage from the existence of the patent right any longer, and thus it is meaningless to invalidate the patent.

Therefore, in such case, it is construed that a legal interest for litigation to rescind a trial decision that dismissed the request for an invalidation trial would also diminish.

D Based on the above fact, under the Patent Act prior to amendment by Act No.36 of 2014, the legal interest for litigation against a trial decision that dismissed a request for an invalidation trial would not be lost in the absence of special circumstances such as the complete loss of possibility of anyone being subjected to a claim for damages or gaining unjust enrichment from, or being imposed criminal penalties for, conduct within the lifetime of patent right even after the expiration of patent right.

E Taking this case into consideration in view of the above fact, there are no special circumstances in this case as described above. Therefore, the legal interest for litigation has not yet been lost.

(2) Further, pursuant to the amendment by Act No.36 of 2014, those who can make a request for an invalidation trial have been limited to only an "interested person," and a patent opposition system that can be made by "anyone" has been introduced instead. Taking this into account, it can't help but construe that a person who is entitled to make a request for an invalidation trial has been currently limited to only a person who has a private proprietary interest with regard to invalidating the patent.

However, as long as there is the slightest possibility that a patent infringement issue may be raised, a person who might possibly get involved with such a problem obviously has a private proprietary interest to invalidate the patent, as well as an interest to make a request for an invalidation trial (therefore, a legal interest for litigation to rescind a trial decision that dismissed the request for an invalidation trial). Therefore, in order to establish the fact that a legal interest for litigation has diminished, it is construed as necessary to find that the possibility of questioning patent right infringement against Plaintiff has been objectively completely lost, and find special circumstances such as the complete loss of possibility of Plaintiff being subjected to a claim for damages or unjust enrichment from, or being imposed criminal penalties for, conduct within the lifetime of patent right and after the expiration of patent right.

2 The Invention

(1) The Invention is set out as in the foregoing No. 2, item 2. The Detailed Description of the Invention of the description (Exhibit Ko 81) has the following description:

A Industrially applicable field

[0001]

The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. More specifically, the invention is effective for the treatment of hypercholesteremia, hyperlipoproteinemia, and further atherosclerosis by specifically inhibiting HMG-CoA reductase, a rate-limiting enzyme of cholesterol biosynthesis, to thereby suppress the synthesis of cholesterols.

B Background Art

[0002]

Hypercholesteremia is a severe risk factor of atherosclerosis, a frequently found cardiovascular disease. Therefore, for the development of novel drug for the treatment of atherosclerosis, it is necessary to investigate the effects on the activity of HMG-CoA reductase, which is a key enzyme for cholesterol synthesis that catalyzes the synthesis of mevalonic acid from 3-hydroxy-3-methyl glutaryl CoA. For such drugs, there are known the first generation HMG-CoA reductase inhibitors, including mevinolin (...), pravastatin (...), and simvastatin (...), which are fungal metabolites or partially modified derivatives thereof. In contrast, recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (...) and BMY 22089 (...) have been developed and are expected as the second generation drugs.

C Problem to be solved by the invention

[0003]

As seen above, the suppression of cholesterol production is essential for the prevention and treatment of atherosclerosis. Taking this into consideration, there is still a need for the development of useful pharmaceutical products.

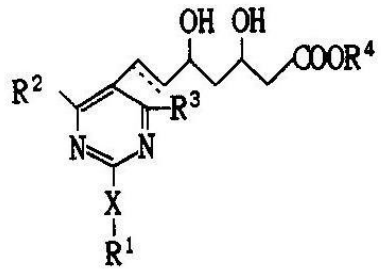
D Means for solving the problem

[0004]

The inventors have investigated in view of the aforesaid situation, and found that the compound represented by the following general formula has an excellent HMG-CoA reductase inhibiting activity, to thereby complete the present invention. Specifically, the present invention relates to an HMG-CoA reductase inhibitor

represented by the formula (I):

[Formula 9]



(wherein R^1 is a lower alkyl, an aryl, or an aralkyl, each of which may have one or more substituents; each of R^2 and R^3 is independently hydrogen, a lower alkyl, or an aryl, and each of said alkyl and aryl may have one or more substituents; R^4 is hydrogen, a lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl group, or imino group which may have a substituent; the dashed line represents the presence or absence of a double bond), or the corresponding ring-closed lactone body.

E Working Examples

[0029]

Working Example 1

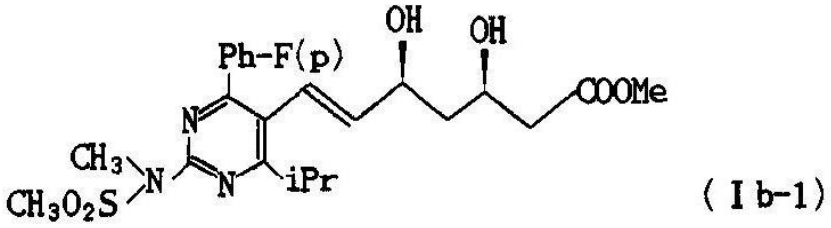
sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ia-1)

...

[0033]

(5) ... methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ib-1) was obtained as 11.4 g of sugar paste (yield: 85.2%).

[Formula 21]



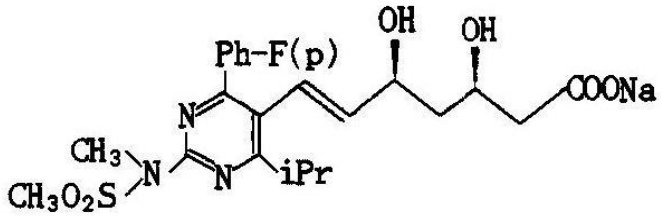
(I b-1)

...

[0034]

(6) To a solution of 11.4 g of the compound (Ib-1) in 160 ml of ethanol, 223 ml of 0.1 N sodium hydroxide was added under ice-cooling. The reaction mixture was gradually warmed to room temperature and stirred for 1 hour. The solvent was distilled off under reduced pressure, and ether was added to the resulting residue and the mixture stirred to give 11.0 g (yield: 95.0%) of the objective compound (Ia-1) as powdery crystals.

[Formula 22]



(Ia-1)

...

[0039]

Working Example 8

Method of synthesizing calcium salt of compound (Ia-1)

Compound (Ia-1) (sodium salt) 1.50 g (3.00 mmol) was dissolved in 15 ml of water and stirred at room temperature under a nitrogen atmosphere. Successively 3.00 ml of 1 mol/L calcium chloride aqueous solution (3.00 mmol) was added dropwise thereto over 3 minutes. The reaction mixture was stirred at the same temperature for 2 hours, and the resulting precipitate was collected, washed with water, and dried to give 1.32 g of calcium salt as powder. This compound started to melt at a temperature of 155°C, but the definitive melting point is ambiguous.

...

[0040]

Biological activity assay

[Test example]

HMG-CoA reductase inhibiting effect

(1) Production method of rat liver microsome

Sprague-Dawley rats, which were given ordinary diets containing 2% cholestyramine and water for 2 weeks ad libitum, were used for the preparation of rat liver microsomes. The thus obtained microsomes were then purified according to the manner described by Kuroda et al., Biochim. Biophys. Acta, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105000 × g was washed once with a

solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). The fraction was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down and kept at -80°C.

[0041]

(2) Measurement method of HMG-CoA reductase inhibiting activity

The rat liver microsome sample (100 μl), which was preserved at -80°C, was fused at 0°C and diluted with 0.7 ml of a cold potassium phosphate buffer (100 mM, pH7.4). This was mixed with 0.8 ml of 50 mM EDTA solution (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100 mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the mixture was kept at 0°C. The microsome solution (1.675 ml) was mixed with 670 μl of 25 mM NADPH solution (buffered with the aforementioned potassium phosphate buffer), and the solution was added to 670 μl solution of 0.5 mM [3-^{14}C]HMG-CoA (3 mCi/mmol). A solution (5 μl) of sodium salt of the test compound dissolved in potassium phosphate buffer was added to 45 μl of the mixture of the microsome and HMG-CoA. The resulting mixture was incubated at 37°C for 30 minutes and cooled. After termination of the reaction by addition of 10 μl of 2N-HCl, the mixture was incubated again at 37°C for 15 minutes. 30 μl of this mixture was applied to thin-layer chromatography on silica gel of 0.5 mm in thickness (manufactured by Merck, Merck AG, trade name: Art 5744). Chromatograms were developed in toluene/acetone (1/1) and the spot, whose Rf value was between 0.45 to 0.60, was scraped. The obtained products were put into a vial containing 10 ml of scintillator to measure specific radio-activity with a scintillation counter. The activities of the compounds of the Invention are shown in Table 4 as comparative data, based on the assumption that the inhibiting activity of Mevinolin (sodium salt) as the reference drug is 100.

[0042]

Table 4

Tested compound	Relative activity
Ia-1	442
Ia-3	385
Ia-5	279

Ia-7	260
Mevinolin Na	100

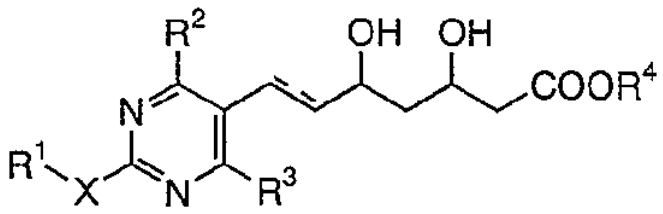
As seen above, it is believed that the compounds of the Invention are particularly effective drugs that exhibit HMG-CoA reductase inhibiting activities superior to that of Mevinolin.

(2) According to the recitation of the scope of claims of the Patent (the aforesaid No. 2, item 2) and the content of the description of the aforesaid item (1), the Invention is recognized as follows:

The Invention relates to a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor effective for the treatment of hypercholesteremia, hyperlipoproteinemia, and furthermore atherosclerosis by specifically inhibiting HMG-CoA reductase, a rate-limiting enzyme of cholesterol biosynthesis to suppress the synthesis of cholesterols ([Claim 12], [0001]).

Mevinolin, Pravastatin, and Simvastatin obtained from fungal metabolites or partially modified derivatives thereof are known as first-generation HMG-CoA reductase inhibitors. Further, recently, synthesized HMG-CoA reductase inhibitors such as fluvastatin and BMY22089 have been developed and are expected as second-generation HMG-CoA reductase inhibitors ([0002]). The suppression of cholesterol production is essential for the prevention and treatment of atherosclerosis. Taking this into consideration, there is still a need for the development of useful pharmaceutical products ([0003]).

The Inventors have found that the compound represented by the following formula (I):



(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with halogen;

R^3 is a lower alkyl;

R^4 is hydrogen or a calcium ion forming hemicalcium salt;

X is an imino group substituted with a alkylsulfonyl group;

the dashed line represents the presence or absence of a double bond)

or its ring-closed lactone body has an excellent HMG-CoA reductase inhibiting activity, and have completed the Invention ([Claim 1], [0004]).

Further, the compound (Ia -1) ([0029], [0034]), which was a "sodium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" ([Claim 2]) encompassed into the Invention, was subjected to the measurement of HMG-CoA reductase inhibiting effect with the measurement method by use of rat liver microsome fraction ([0040], [0041]). It had a relative activity of 442, with the inhibiting activity of sodium salt of Mevinolin given as 100. Therefore, it is believed that the compound of the Invention is an effective drug that exhibits HMG-CoA reductase inhibiting activities superior to that of Mevinolin ([0042]).

3 Ground 1 for rescission

(1) Determination of inventive step

Article 29, paragraph (1) of the Patent Act specifies that "An inventor of an invention that is industrially applicable may be entitled to obtain a patent for said invention, except for the following cases." and as the case of item (iii), it specifies "inventions that were described in a distributed publication" "in Japan or a foreign country prior to the filing of the patent application." Article 29, paragraph (2) specifies that an invention easily conceivable before the filing of the invention by a person ordinarily skilled in the art on the basis of an invention provided in each item of Article 29, paragraph (1) should not be granted a patent, which specifies that an invention not involving inventive step cannot be granted a patent.

The above inventive step requirement is established by finding an invention according to patent application (hereinafter referred to as "the present invention") on the basis of the scope of claims, comparing the invention with a certain invention provided in each item of Article 29, paragraph (1) of the Patent Act, finding a common feature and a difference, and if there is a difference, determining whether a person ordinarily skilled in the art could easily conceive of the present invention corresponding to the difference on the basis of the state of the art as of the filing (or priority) date. The same shall apply to "3 Ground 1 for rescission."

In the determination of such inventive step, a certain invention provided in each

item of Article 29, paragraph (1) of the Patent Act to be compared with the present invention (hereinafter referred to as "the primarily cited invention," and referred to as "cited invention" together with the following "auxiliary cited invention") is usually selected from the inventions that are relevant to the present invention in their technical field and falling within a range where a person ordinarily skilled in the art in the technical field targets for consideration. In particular, "an invention described in a Publication" of Article 29, paragraph (1), item (iii), should be a basis for the determination of whether a person ordinarily skilled in the art could easily conceive of the present invention on the basis of the state of the art as of the filing. Therefore, it must be a specific technical concept to be extracted from the description of a Publication. Further, if a compound is described in a form of a general formula in a publication and the general formula has an enormous number of alternatives, a person ordinarily skilled in the art fails to extract a specific technical concept according to a specific alternative from the description of the publication in the absence of circumstances where the specific technical concept according to the specific alternative should be positively or preferentially selected.

Therefore, it is reasonable to find that, if an invention as allegedly claimed to be a cited invention is the "invention described in a publication" and a compound is described in a form of general formula in the publication and the general formula has an enormous number of alternatives, a specific technical concept according to a specific alternative cannot be extracted in the absence of circumstances where the technical concept according to the specific alternative should be positively or preferentially selected, and such invention is not qualified for a cited invention.

This logic shall also apply to the finding of, from publications, an auxiliary cited invention, which is another "invention described in a publication" provided in Article 29, paragraph (1), item (iii) corresponding to a difference between the present invention and the primarily cited invention (hereinafter referred to as "the auxiliary cited invention"), in the case of determining whether the present invention is easily conceivable by applying the auxiliary cited invention to a primarily cited invention. Therefore, it is reasonable to find that, if an auxiliary cited invention is the "invention described in a publication" and a compound is described in the form of a general formula in the publication and the general formula has an enormous number of alternatives, a specific technical concept according to a specific alternative cannot be extracted in the absence of circumstances where the specific technical concept according to the specific alternative should be positively or preferentially selected, and such invention is not qualified for an auxiliary cited invention.

Further, as aforementioned, in the case of determining whether the present invention is easily conceivable by applying the auxiliary cited invention to a primarily cited invention, it is determined by: [i] Comprehensively considering the suggestions in a primarily cited invention or an auxiliary cited invention, the relevance in technical field, and the commonality in problem, effect, and function, a determination is made as to whether there is a motivation to apply the auxiliary cited invention to the primarily cited invention and arrive at the present invention, and [ii] Considering the presence or the absence of factors inhibiting the application as well as the presence or the absence of unexpected significant effects in combination. In a suit for the rescission against a trial decision of trial for invalidation of a patent, it is a person who argues invalidation of patent (in a suit for the rescission against a trial decision of appeals against an examiner's decision of refusal and a suit for the rescission of the decision of revoke according to the opposition to a granted patent, it is the commissioner of the Japan Patent Office) for the above [i]; and a patentee (in a suit for the rescission against a trial decision of appeals against an examiner's decision of refusal, it is a patent applicant) for the above [ii] that is required to argue and establish the facts that underlie the existence of these factors.

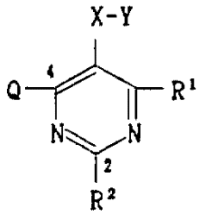
(2) Exhibit Ko 1 Invention

A Content of Exhibit Ko 1

Exhibit Ko 1 (National Publication of International Patent Application No. 1991-501613) has the following descriptions:

(A) The scope of claims

"1. A compound of formula I in free acid form,

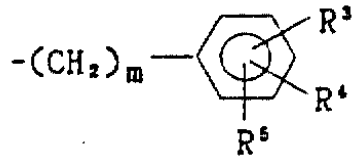


I

wherein R^1 and R^2 independently are:

a C_{1-6} alkyl not containing an asymmetric carbon atom;

a C_{3-6} cycloalkyl; or



wherein

m is 0, 1, 2, or 3;

R^3 is hydrogen, a C_{1-3} alkyl, n-butyl, i-butyl, t-butyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy, or benzyloxy;

R^4 is hydrogen, a C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy; and R^5 is hydrogen, a C_{1-2} alkyl, C_{1-2} alkoxy, fluoro or chloro; with the provisos that

not more than one of R^3 and R^4 is trifluoromethyl;

not more than one of R^3 and R^4 is phenoxy; and

not more than one of R^3 and R^4 is benzyloxy; or

R^1 is as defined above, and

R^2 is benzyloxy;

benzylthio;

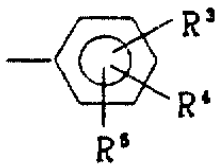
$-N(R^8)_2$ wherein either each R^8 independently is a C_{1-4} alkyl not containing an asymmetric carbon atom or both R^8 together with the nitrogen atom form part of a 5-,6- or 7-membered optionally substituted ring optionally containing one or more further heteroatoms (ring B);

or Q wherein

Q is Q' or Q'' wherein

Q' is a heterocyclic group optionally mono- or independently di-substituted by C_{1-2} alkyl or C_{1-2} alkoxy and

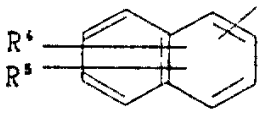
Q'' is: Q''a, with the proviso that Q''a is



where R^3, R^4, and R^5 are as defined above, including the provisos thereto;

or

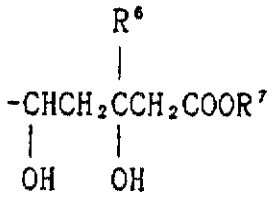
Q''b, with the provisos that Q''b is



where R^4 and R^5 are as defined above;

X is either ethylene or vinylene; and

Y is: a group Y' of formula

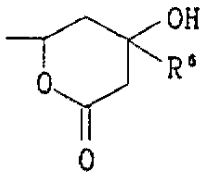


wherein

R^6 is hydrogen or a C_{1-3} alkyl; and

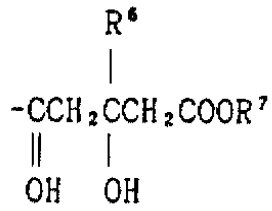
R^7 is hydrogen, an ester group ($R^{7'}$), or a cation (M)

; a group Y" of formula



where R^6 is as defined above

: or a group Y'" of formula



where R^6 and R^7 are as defined above

: with the proviso that

when Y is a group Y'",

then X is vinylene and/or R^6 is a C_{1-3} alkyl; in free acid form, or in the form of an ester or δ-lactone thereof, or in salt form as appropriate." (Claim 1 of the scope of claims)

(B) Description (page 11, right bottom column, line 9 to page 12, left upper column, line 13)

"In particular the compounds show activity in the following tests:

Test A. In vitro microsomal assay of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition: as described in EP 114027:

The following results are obtained by test A:

Product of Working Example 11d: IC_{50}=0.039 μM;

Product of Working Example 1b): IC_{50}=0.026 μM;

Compactin: IC_{50} = 1.01 μM;

Mevinolin: IC_{50} = 0.352 μM.

IC_{50} is the concentration of the test substance in the assay system calculated to produce a 50% inhibition of HMG-CoA reductase activity. The tests are run at concentrations of test substance between 0.05 μM and 1000 μM.

Test B. In vivo cholesterol biosynthesis inhibition test: as described in EP 114027:

The following results are obtained by test B:

Product of Working Example 11d: ED_{50}=0.04 mg/kg;

Product of Working Example 1b): ED_{50}=0.028 mg/kg;

Compactin: ED_{50} = 3.5 mg/kg;

Mevinolin: ED_{50} = 0.41 mg/kg.

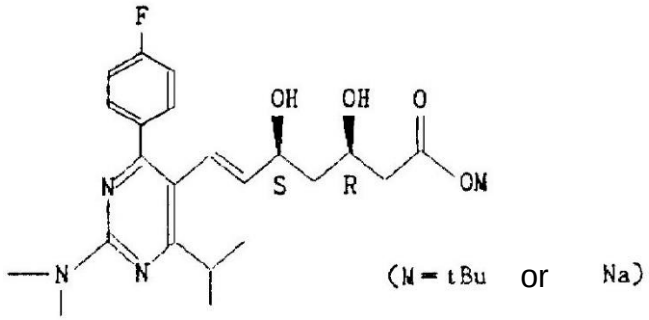
ED_{50} is the dose of the test substance calculated to produce a 50% inhibition of 3β-hydroxysterol synthesis. The tests are run to test doses of between 0.01 mg/kg and 10 mg/kg.

The above test data indicate that the compounds are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the rate limiting enzyme in cholesterol biosynthesis, and, therefore, they are inhibitors of cholesterol biosynthesis. Consequently, they are indicated for use in lowering the blood cholesterol level in animals, e.g. mammals, especially larger primates, and, therefore, are indicated for use as hypolipoproteinemic and anti-atherosclerotic agents."

(C) Description (page 12, left bottom column, line 3 to page 13, left upper column, line 3)

"Working Example 1: (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid, (1,1-dimethylethyl) ester; and sodium salt

(R^1 = isopropyl; R^2 = dimethylamino; Q = 4-fluorophenyl; X = (E)-CH = CH-; Y = group Y', wherein R^4 = H, R^7 = tert-butyl or Na and the steric configuration is 3R, 5S) [(Method c) (Deprotection) and recycle in a salt form]



a) Deprotection:

14.2 g of (3R,5S)-[E]-3,5-bis[[(1,1-dimethylethyl)-diphenylsilyl]oxy]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-(dimethylamino)pyrimidin-5-yl]-6-heptenoic acid, 1,1-dimethylethyl ester (see below) dissolved in 350 ml of CH_3CN was added to a mixture of 47.2 g of tetra-n-butylammonium fluoride trihydrate and 350 ml of acetonitrile and 9 g (8.6 ml) of glacial acetic acid. This was stirred at 45-50°C under argon, and then stirred at 65°C for 24 hours. The reaction mixture was poured into 150 ml of saturated sodium chloride solution, 200 ml of saturated sodium carbonate solution, and 1.35 liters of water (the pH was approximately 7.5-8.5 after the addition) and the mixture was extracted three times with diethyl ether. The diethyl ether extracts were combined, washed three times with 500 ml portions of water, dried over anhydrous $MgSO_4$, filtered, and evaporated at a reduced pressure to yield an oil. The crude product was flash chromatographed on a 230-400 ASTM silica gel using 6:4 mixed hexanes:ethyl acetate as the eluant. A yellow oil was isolated, and then triturated to a light yellow powder with hexanes. (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-(dimethylamino)pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, (1,1-dimethylethyl) ester was obtained (M.P. 114-116°C; 25[α] D = + 7.7°, $CHCl_3$)

b) Hydrolysis:

12.35 g of the product of step a) above, 26.0 ml of 1N NaOH, and 150 ml of ethanol were combined and stirred at room temperature for 3-4 hours. The solvent was rotary evaporated. The residue was treated with approximately 150 ml of toluene and the toluene rotary evaporated. This was repeated, and the final residue was triturated to a light yellow solid with a mixture of hexane-ether. This was filtered and dried to yield sodium (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-

(dimethylamino)pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoate (M.P. 231-233°C; 25[α]D = +33.3°, c = 20.625 mg in 1 ml H_2O)."

(D) Description (page 20, left bottom)

"Working Example 11

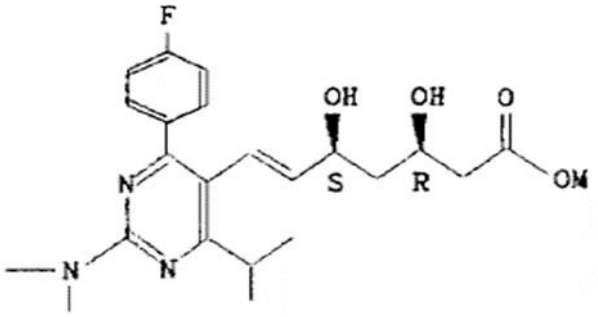
In a similar manner to Working Example 5 (hydrolysis), starting from esters corresponding to Working Example 9 or 10, the following sodium salt was obtained.

Sub-example No.	R^1	R^2	Q	X	Y	Starting from esters of the following No.	Melting point
11a	isopropyl	isopropyl	4-pyridyl	(E)-CH=CH-	Y', with the provisos that R^6=H, R^7=ethyl, and steric configuration is mainly erythro (>98%) (racemic body)	9	224 to 225°C (decomposed)
11b	isopropyl	tert-butyl	4-pyridyl	(E)-CH=CH-	Y'	10a	
11c	isopropyl	methyl	4-pyridyl	(E)-CH=CH-	Y'	10b	
11d	isopropyl	-$N(CH_3)_2$	4-pyridyl	(E)-CH=CH-	Y'	10c	
11e	isopropyl	tert-butyl	4-fluorophenyl	(E)-CH=CH-	Y'	10d	foam (NMR[1)])
11f	isopropyl	methyl	4-fluorophenyl	(E)-CH=CH-	Y'	10e	foam (NMR[2)])
11g	isopropyl	isopropyl	4-fluorophenyl	(E)-CH=CH-	Y'	10f	172 to 178°C (decomposed)
11h	isopropyl	-$N(CH_3)_2$	4-fluorophenyl	(E)-CH=CH-	Y'	10g	210 to 212°C (decomposed)
11i	methyl	methyl	4-fluorophenyl	(E)-CH=CH-	Y'	10h	foam (NMR[3)])

"

B Finding of Exhibit Ko 1 Invention

According to the aforesaid A, Exhibit Ko 1 Invention is recognized as "



a compound of (M=Na)"

as in the finding of the trial decision. In this respect, there is no dispute between the parties.

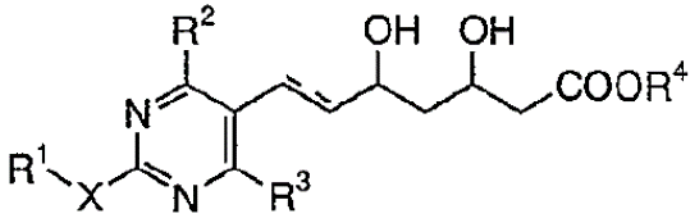
(3) Selection of primarily cited invention

As discussed in the aforesaid item 2(2), the Invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor effective for the treatment of hypercholesteremia, hyperlipoproteinemia, atherosclerosis by specifically inhibiting HMG-CoA reductase, a rate-limiting enzyme of cholesterol biosynthesis, to thereby suppress the synthesis of cholesterols. As discussed in the aforesaid item (2)A, the Exhibit Ko 1 Invention also relates to a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), a rate-limiting enzyme for the biosynthesis of cholesterols, and relates to a treating agent for hypolipoproteinemic and anti-atherosclerotic agents that decrease a blood cholesterol level. Therefore, it has a technical field in common with the Invention, and falls within a range where a person ordinarily skilled in the art in a technical field to which the Invention pertains would consider.

Further, comparing Invention 1 and the Exhibit Ko 1 Invention as is found in the aforesaid item (2)B, they are common in the following [Common features] as in the finding of the trial decision. In this regard, there is no dispute between the parties, and thus they have similar structures. Therefore, the Exhibit Ko 1 Invention is comparable in structures to the Invention.

[Common features]

"A compound represented by the following formula (I):



(where

R^1 is a lower alkyl;

R^2 is a phenyl substituted with a halogen;

R^3 is a lower alkyl;

the dashed line represents the presence or absence of a double bond.)

or a ring-closed lactone body thereof"

Consequently, the Exhibit Ko 1 Invention is an underlying publicly known technical idea in considering the inventive step of the Invention.

Based on the above fact, the Exhibit Ko 1 Invention is not construed as being not qualified for the primarily cited invention in the determination of the inventive step of Article 29, paragraph (2) of the Patent Act with respect to the Invention. The argument presented by Defendant and others opposed to this is not acceptable.

(4) Comparison

Here, comparing Invention 1 and the Exhibit Ko 1 Invention as is found in the aforesaid item (2)B, they are common in the [Common features] as in the finding of the trial decision, as mentioned in the aforesaid item (3), and they are different in the following [Difference]: In this respect, there is no dispute between the parties.

[Difference]

(1-i)

In the Invention 1, X is an imino group substituted with an alkylsulfonyl group, whereas in the Exhibit Ko 1 Invention it is an imino group substituted with a methyl group

(1-ii)

In the Invention 1, R^4 is hydrogen or a calcium ion forming hemicalcium salt, whereas in the Exhibit Ko 1 Invention it is a sodium ion forming sodium salt

(5) Determination of differences between Invention 1 and the Exhibit Ko 1

Invention

A Determination whether or not the Difference (1-i) from the cited invention can be easily conceived

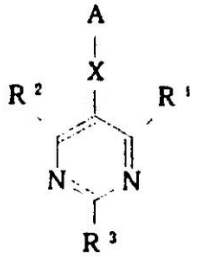
(A) Regarding the difference (1-i), Plaintiffs argue that the Invention 1 is easily conceivable by combining the Exhibit Ko 1 Invention with the Exhibit Ko 2 Invention, specifically by replacing one of two methyl groups ($-CH_3$) of the dimethylamino group ($-N(CH_3)_2$) at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with an alkylsulfonyl group ($-SO_2R'$(R' is an alkyl group)) of the Exhibit Ko 2 Invention; i.e., a "dimethylamino group" at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with "$-N(CH_3)(SO_2R')$.

Accordingly, the Exhibit Ko 2 Invention is considered in the following.

(B) a Exhibit Ko 2 (Japanese Unexamined Patent Application Publication No. 1989-261377) has the following descriptions:

(a) Scope of claims

"1. A substituted pyrimidine of the general formula:



(I)

where R^1 represents a cycloalkyl or

alkyl, and the group may be substituted with a halogen, cyano, alkoxy, alkylthio, alkylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl, alkoxycarbonyl, or acyl group, or formula $-NR^4R^5$, supposing that R^4 and R^5 are the same or different from each other and represent an alkyl, aryl, aralkyl, acyl, alkylsulfonyl, or arylsulfonyl,

or may be substituted with a carbamoyl, dialkylcarbamoyl, sulfamoyl, dialkylsulfamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulfonyl, aralkoxy, aralkylthio or aralkylsulfonyl, and the substituent groups of heteroaryl and aryl group mentioned last may be substituted with one, two, or three substituent groups that are the same or different from each other consisting of a halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio, or alkylsulfonyl,

R^2 represents a heteroaryl, and the group may be substituted with one, two, or

three groups, the same or different from each other, consisting of halogen, alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsufonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or alkoxycarbonyl, or formula -NR^4R^5, with the provisos that R^4 and R^5 are as described above, or

R^2 represents an aryl, and the group may be substituted with one to five groups, the same or different from each other, consisting of an alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsufonyl, aralkyl, aralkoxy, aralkylthio, aralkylsufonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulfamoyl, dialkylsulfamoyl, carbamoyl, or dialkylcarbamoyl, or formula -NR^4R^5, with the provisos that R^4 and R^5 are as described above, R^3 represents hydrogen,

a cycloalkyl or

alkyl, and the group may be substituted with a halogen, cyano, alkoxy, alkylthio, alkylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl, alkoxycarbonyl, or acyl group, or formula -NR^4R^5, with the provisos that

R^4 and R^5 are as described above,

or may be substituted with a carbamoyl, dialkylcarbamoyl, sulfamoyl, dialkylsulfamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulfonyl, aralkoxy, aralkylthio, or aralkylsulfonyl, and the substituent groups of heteroaryl and aryl group mentioned last may be substituted with one, two, or three groups that are the same or different from each other consisting of a halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio, or alkylsulfonyl, or

R^3 represents a heteroaryl, and the group may be substituted with one, two, or three groups that are the same or different from each other, consisting of a halogen, alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsufonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or alkoxy, or the formula -NR^4R^5, with the provisos that

R^4 and R^5 are as described above,

or

R^3 represents an aryl, and the group may be substituted with one to five groups, the same or different from each other, consisting of an alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsufonyl, aralkyl, aralkoxy, aralkylthio, aralkylsufonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulfamoyl, dialkylsulfamoyl, carbamoyl, or dialkylcarbonyl, or formula -NR^4R^5, with the provisos that R^4 and R^5 are as described

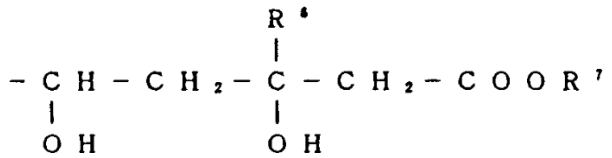
above, or

R^3 represents an alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, or aralkylthio, or a group formula $-NR^4R^5$, supposing that

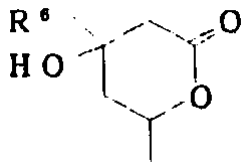
R^4 and R^5 are as described above,

X represents a group of formula $-CH_2-CH_2-$ or -CH=CH-, and

A represents the formula or a group, wherein



or



R^6 represents hydrogen or an alkyl, and

R^7 represents hydrogen,

or a methyl, aralkyl, or aryl group, or a cation."

(b) Detailed Explanation of the Invention (page 6, left bottom column, lines 2 to 5)

"Surprisingly, the substituted pyrimidine of the present invention shows a good inhibiting effect in HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase)."

(c) Detailed Description of the Invention (page 8, right upper column, line 11 to left bottom column, line 7)

"When R^7 represents a cation, it preferably means a physiologically acceptable metal cation or ammonium cation. In this regard, preferable ones include: alkali metals or alkali earth metals, e.g. a sodium cation, potassium cation, magnesium cation, or calcium cation, and aluminum cation or ammonium cation, and non-toxic ammonium cations substituted with amines usable for the production of salts: e.g. di-loweralkylamines (C_1 to about C_6), tri-loweralkylamines (C_1 to about C_6), dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-β-phenylethylamine, N-methylmorphorine, N-ethylmorphorine, dihydroabiethylamine, N,N'-bis-

diehydroabiethylethylenediamine, N-loweralkylpyperidine, and the other amines."

(d) Detailed Description of the Invention (page 10, left upper column, line 9 from the bottom to page 11, right bottom column, line 10)

"A particularly preferable compound of the general formula (I) is a compound where

R^1 represents a cyclopropyl, cyclopentyl or cyclohexyl, or methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl, each may be substituted with fluorine, chlorine, bromine, cyano, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzoyl, acetyl, pyridyl, pyrimidyl, thienyl, furyl, phenyl, phenoxy, phenylthio, phenylsulfonyl, benzyloxy, benzylthio, or benzylsulfonyl,

R^2 represents a pyridyl, pyrimidyl, quinolyl, or isoquinolyl, the groups may be substituted with fluorine, chlorine, methyl, methoxy, or trifluoromethyl, or

R^2 represents a phenyl, and the group may be substituted with one, two, or three groups that are the same or different from each other, consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, phenyl, phenoxy, benzyl, benzyloxy, fluorine, chlorine, bromo, cyano, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert-butoxycarbonyl,

R^3 represents hydrogen, a cyclopropyl, cyclopentyl, or cyclohexyl, or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, or, isohexyl, and these groups include fluorine, chlorine, bromine, a cyano, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert-butoxycarbonyl, benzoyl, acetyl or ethylcarbonyl, or the formula $-NR^4R^5$, with the provisos that

R^4 and R^5 are the same or different from each other, and represent a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, phenyl, benzyl, acetyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, or phenylsulfonyl,

or may be substituted with a pyridyl, pyrimidyl, pyradinyl, pyridazinyl, quinoline, isoquinoline, thienyl, furyl, phenyl, phenoxy, phenylthio, phenylsulfonyl, benzyloxy, benzylthio, or benzylsulfonyl, the above heteroaryl and aryl groups may be substituted with fluorine, chlorine, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, trifluoromethyl, or trifluoromethoxy,

or

R^3 represents a thienyl, furyl, pyridyl, pyrimidyl, pyradinyl, pyridazinyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, quinolyl, isoquinolyl, benzoxazolyl, benzimidazolyl, or benzthiazolyl, wherein these groups may be substituted with fluorine, chlorine, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert-butoxycarbonyl, or

R^3 represents a phenyl, and the group may be substituted with one, two, or three groups that are the same or different from each other, consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, phenyl, phenoxy, phenylthio, phenylsulfonyl, benzyl, benzyloxy, benzylthio, benzylsulfonyl, fluorine, chlorine, bromo, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert-butoxycarbonyl or the group $-NR^4R^5$, with the provisos that

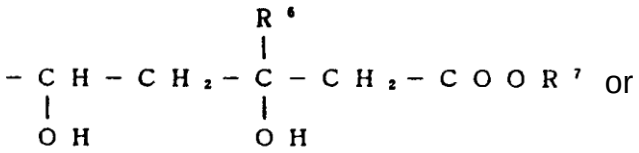
R^4 and R^5 are as described above,

or

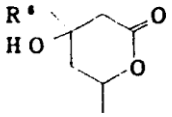
R^3 represents an alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, or aralkylthio, or the formula $-NR^4R^5$, with the provisos that R^4 and R^5 are as described above,

X represents a group of formula $-CH_2-CH_2-$ or -CH=CH-, and

A is a group represented by the formula:



or



wherein

R^6 represents hydrogen, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl, and

R^7 represents hydrogen, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl, or benzyl, or sodium, potassium, calcium, magnesium, or ammonium ion."

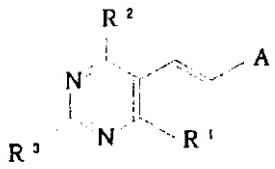
(e) Detailed Description of the Invention (page 11, right bottom column, line 11 to page 12, right upper column, line 8. [excluding the lines described in the drawing; the same shall apply hereinafter]):

"Substituted pyrimidine of the general formula (I) of the present invention has a few asymmetric carbon atoms, and thus various stereochemical types. The present invention relates to both individual isomers and a mixture of isomers.

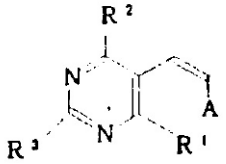
Different stereoisomers generate according to what the group X or the group A represents. This is further elaborated in the following:

a) If the group -X- represents the group of formula -CH=CH-, the compound of the present invention may be present in two stereoisomer forms of E steric configuration (II) and Z steric configuration (III) in double bond:

(II) E-type



(III) Z-type

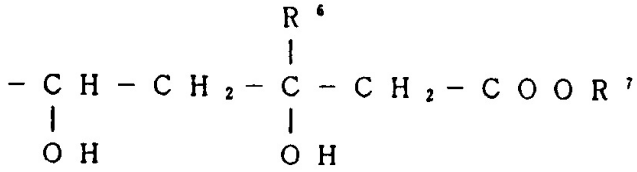


where R^1, R^2, R^3, and A are as described above.

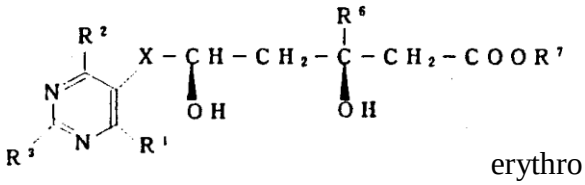
E steric configuration (II) is preferable for the compound of the general

formula (I).

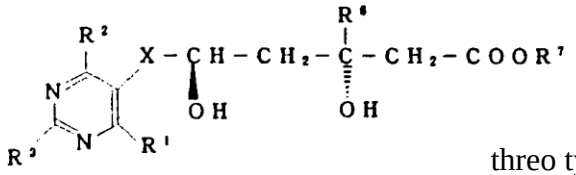
b) If a group -A- represents the group of the following formula:



the compound of general formula (I) has at least two asymmetric carbon atoms; i.e. two carbon atoms to which hydroxyl group binds. According to a relative position of these hydroxyl groups, the compound of the present invention may be present in either erythro steric configuration (IV) or threo steric configuration (V).



erythro type (IV)



threo type (V)

Further, in both cases of the compounds with erythro and threo steric configurations, there are two kinds of enantiomers; i.e. 3R,5S-isomer or 3S,5R-isomers (erythro type) and 3R,5R-isomer and 3S,5S-isomer (threo type).

In this regard, an isomer with erythro steric configuration is preferable, and 3R,5S-isomer and a 3R,5S-3S,5R-racemic body is particularly preferable."

(f) Detailed Description of the Invention (page 13, right upper column, line 1 to left bottom column, line 7)

"Particularly, the most preferable compound of the general formula (Ia) and (Ib) is the compound where

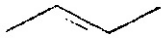
R^1 represents a cyclopropyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl, and

R^2 represents phenyl that may be mono- or di-substituted with the same or different groups consisting of a methyl, methoxy, phenoxy, fluorine, chlorine, or trifluoromethyl,

R_3 represents a methyl, isopropyl, tert-butyl, or phenyl that may be mono- or di-

substituted with the same or different groups consisting of methyl, methoxy, fluorine or chlorine,

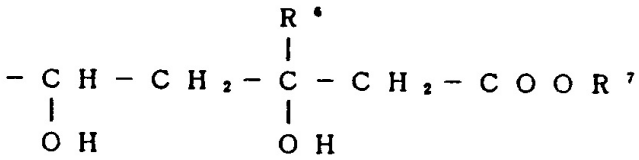
X is a group represented by the formula:



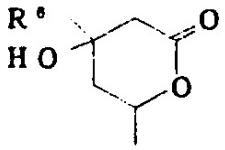
(E steric configuration)

and

A is represented by the formula:



or



where, R^6 represents hydrogen, and

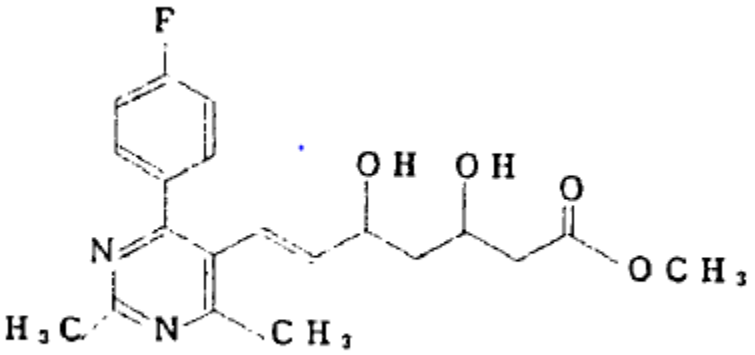
R_7 represents hydrogen, a methyl or ethyl, or a sodium or potassium cation."

(g) Detailed Description of the Invention (Working Examples)

i Working Example 8 (page 22, left bottom column, lines 12 to 15)

"Working Example 8

methylerythro-(E)-3,5,-dihydroxy-7-[2,6-dimethyl-4-(4-fluorophenyl)-pyrimid-5-yl]-hept-6-enoate

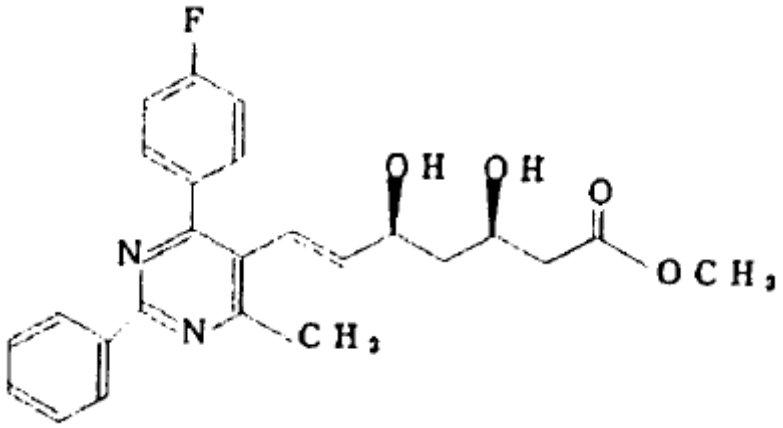


"

ii Working Example 15 (page 24, right upper column, lines 1 to 5)

"Working Example 15

methylerythro(E)-3,5,-dihydroxy-7-[4-(4-fluorophenyl)-6-methyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate

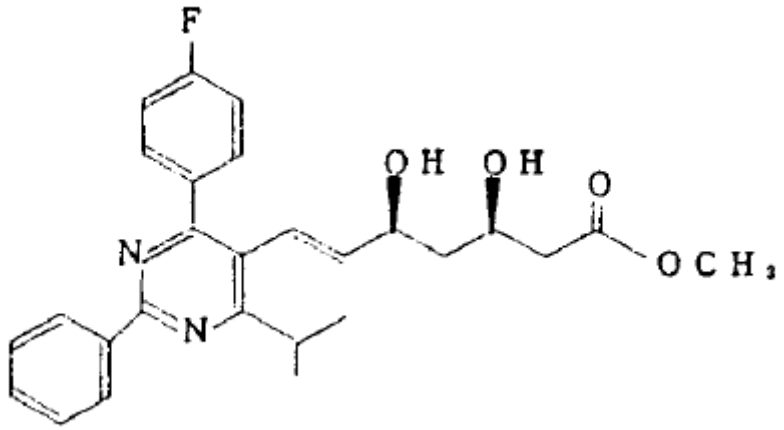


"

iii Working Example 23 (page 26, left upper column, line 5 to last line from the bottom)

"Working Example 23

methylerythro-(E)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-6-isopropyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate



"

iv Working Example 24 (page 26, right upper column, line 6 from the bottom to page 27, left upper column, line 10)

"Use working example

Working Example 24

Enzymatic activity was measured in accordance with the modification by Ness, etc. to measure a relative suppression capability, with the IC_{50} value of a control substance of Mevinolin given as 1, and compared with an IC_{50} value of test compound measured simultaneously.

The active compounds of Working Examples 1 to 23 showed a higher effect compared to Mevinolin."

b According to the aforesaid a, Exhibit Ko 2 describes a compound represented by general formula (I). The compound has a pyrimidine ring, and substituent groups at the 2-, 4-, and 6-positions of the pyrimidine ring, and shows good inhibiting effects in HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase).

(C)a As in the aforesaid item (B), the compound of general formula (I) of Exhibit Ko 2 is intended to provide an HMG-CoA reductase inhibitor, like the compound of general formula I of Exhibit Ko 1. They are common in that they have a pyrimidine ring and substituent groups at the 2-, 4-, and 6-positions of the pyrimidine ring. The compound of the Exhibit Ko 1 Invention is encompassed into the compound represented by general formula (I) of Exhibit Ko 2.

Exhibit Ko 2 describes "$-NR^4R^5$" as an alternative of substituent group R^3 at the 2-position of the pyrimidine ring of a "particularly preferable compound" among the compounds represented by general formula (I) of Exhibit Ko 2, and also describes "methyl group" and "alkylsulfonyl group" as an alternative for R^4 and R^5.

Plaintiffs did not particularly argue however, that there are numerous alternatives of R^3 in "particularly preferable compound" of Exhibit Ko 2, and the number is at least 20 million. The compound where R^3 is "$-NR^4R^5$, and R^4 and R^5 are "methyl" and "alkylsulfonyl" is one alternative among 20 million or more.

Further, Exhibit Ko 2 not only describes "particularly preferable compound" but also "particularly extremely preferable compound," which fails to describe "$-NR^4R^5$" as an alternative of R^3.

Furthermore, Exhibit Ko 2 describes Working Example 8 (R^3 is methyl), Working Example 15 (R^3 is phenyl), and Working Example 23 (R^3 is phenyl) as working examples of the compound having the same structure as the Exhibit Ko 1 Invention in X and A of the general formula (I) of Exhibit Ko 2. It fails to describe "$-NR^4R^5$" for R^3.

Consequently, although Exhibit Ko 2 describes an alkylsulfonyl group, it is

impossible for a person ordinarily skilled in the art to find from the description of Exhibit Ko 2 any circumstances where "-NR^4R^5" is positively or preferentially selected as R^3 of the general formula (I) of Exhibit Ko 2. It is difficult to find any circumstances to select "-NR^4R^5, and further select "methyl" and "alkylsulfonyl" for R^4 and R^5.

Therefore, it cannot be seen that the technical idea of changing the group at the 2-position of the pyrimidine ring into "-$N(CH_3)(SO_2R')$" may be extracted from Exhibit Ko 2. It cannot be said that Exhibit Ko 2 describes the structure according to the above difference (1-i). The combination of the Exhibit Ko 1 Invention with the Exhibit Ko 2 Invention may not result in the structure according to the difference (1-i) of the Invention.

b Plaintiffs argue that Exhibit Ko 2 describes a method of producing the whole range of the compounds of general formula (I) and HMG-CoA reductase inhibiting activity as in the following, and it can thus be seen as a technical support of the compound of the general formula (I) where "NR^4R^5" was selected for "R^3, and therefore the finding of the trial decision to the effect that " Exhibit Ko 2 fails to describe a producing method thereof, nor pharmacological tests of HMG-CoA reductase inhibiting activity with respect to compounds where 'NR^4R^5' was selected for 'R^3'" is erroneous.

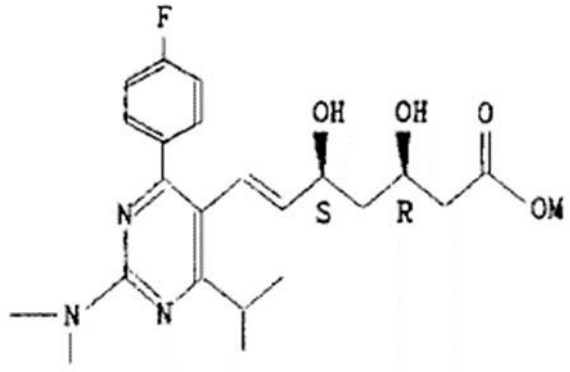
As in the aforesaid item a, the compound represented by general formula (I) of Exhibit Ko 2 is intended to provide a HMG-CoA reductase inhibitor. As in the aforesaid item (B)a(g), Exhibit Ko 2 discloses that the compounds of Working Examples 1 to 23 of Exhibit Ko 2 encompassed in the compound represented by general formula (I) of Exhibit Ko 2 have a higher HMG-CoA reductase inhibiting activity compared to Mevinolin. Further, Exhibit Ko 16 discloses that a specific compound within the general formula (I) of Exhibit Ko 2 has an HMG-CoA reductase inhibiting activity, and according to the evidences (Exhibit Ko 16, and Ko 73 to Ko 75) and the entire import of the oral argument, it is recognized that a person ordinarily skilled in the art sometimes recognizes that a specific compound in which only a part of the working example of Exhibit Ko 2 is changed is likely to have an HMG-CoA reductase inhibiting activity.

However, Working Examples 1 to 23 of Exhibit Ko 2 and the specific compound of the above finding do not include a compound with a sulfonamide structure. According to the evidence (Exhibit Otsu 65) and the entire import of the oral argument, it is a matter of common general technical knowledge that chemical

substances possibly undergo change of their effects by a very small structural change. Not all of numerous compounds represented by general formula (I) of Exhibit Ko 2 are expected to have an HMG-CoA reductase inhibiting activity comparable to or higher than those of Working Examples 1 to 23 or the specific compound in the above finding. It is also possible to lose the HMG-CoA reductase inhibiting activity.

Therefore, it cannot be seen from Exhibit Ko 2 that all of numerous compounds represented by general formula (I) of Exhibit Ko 2 are technically supported. The above argument by Plaintiffs does not affect the determination of the aforesaid item a.

(D)a Even if Exhibit Ko 2 might be evaluated as describing the structure according to the difference (1-i), as in the aforesaid item (2), a compound of Exhibit Ko 1 Invention of "a compound of



(M=Na)" "sodium (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid" is a product of Working Example 1b) of Exhibit Ko 1 with an HMG-CoA reductase inhibiting activity, and is encompassed into the compound represented by the general formula I of Exhibit Ko 1. Further, Exhibit Ko 1 describes "-$N(R^8)_2$" as an alternative of substituent group R^2 at the 2-position of the pyrimidine ring of formula I of Exhibit Ko 1. Furthermore, it describes "methyl group" as an alternative of R^8, but it fails to describe "alkylsulfonyl group" as an alternative of R^8.

Consequently, it cannot be said that Exhibit Ko 1 has a motivation to replace "dimethylamino group" at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with "-$N(CH_3)(SO_2R')$," which is not included in the alternatives of formula I of Exhibit Ko 1.

b(a) It was recognized as a matter of common general technical knowledge of a person ordinarily skilled in the art as of the priority date that the most cholesterols are synthesized by the liver, and HMG-CoA reductase catalyzes the biosynthesis of

cholesterols, and HMG-CoA reductase inhibitor inhibits the biosynthesis of cholesterols (Exhibit Ko 7, Ko 10, Ko 11, and Ko 14).

"Many discussions are made on articles with regard to the properties and the presence or the absence of tissue (liver) selectivity of various HMGR (HMG-CoA reductase) inhibitors" as of the priority date (Exhibit Ko 7). Further, there was a finding that "Lovastatin and Simvastatin encompassed into HMG-CoA reductase inhibitors might cause cataract in dog at high dose" (Exhibit Ko 24).

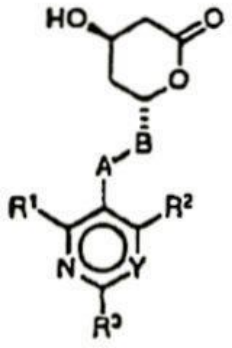
Consequently, it can be said that a person ordinarily skilled in the art could recognize the technical problem as of the priority date to obtain an HMG-CoA reductase inhibitor with high selectivity by the liver, by which most cholesterols are synthesized, in view of the side effects.

(b) Exhibit Ko 7 (According to the entire import of the oral argument, it was published on January 1, 1991.) discloses that, considering a hypothesis of "tissue selectivity is mainly affected by relative lipophilicity of drug, and a compound with relatively high hydrophilicity in an HMG-CoA reductase inhibitor may possibly improve liver selectivity" with respect to the compound of HMG-CoA reductase inhibitors such as Lovastatin and Pravastatin, "A 'cross' point where the selectivity becomes equal in the liver and other tissue is CLOGP≈2," and "below this level, the compound is liver-selective, and above this level, the compound is peripheral tissue-selective." Further, Exhibit Ko 20 discloses that the lipophilicity (logP) of four HMG-CoA reductase inhibitors of Pravastatin, Lovastatin, Mevastatin, and Simvastatin was measured, and Pravastatin with a hydroxyl group has a lower logP value compared to Lovastatin and Simvastatin with a methyl group at the 6-position of hexahydronaphthalene ring, and Pravastatin is not so effectively taken by cells outside the liver due to such physiochemical properties.

It can be deduced from the description of Exhibit Ko 7 and Ko 20 that a compound with relatively high hydrophilicity in an HMG-CoA reductase inhibitor may possibly improve liver selectivity. Thus a person ordinarily skilled in the art could recognize a motivation as of the priority date to assess the compound showing HMG-CoA reductase inhibiting activity with an indicator of hydrophilicity and select a compound with high hydrophilicity (logP of 2 or less) in order to obtain an HMG-CoA reductase inhibitor with high selectivity for the liver in view of side effects.

(c) On the other hand, Exhibit Ko 16, which describes the HMG-CoA reductase inhibiting activity of lactone of pyridine and pyrimidine substituted 3,5-

dihydroxy-6-heptenoic acid, discloses that the bulky, lipophilic substituent group at the 6-position of the central aromatic ring greatly contributes to biological activity of synthetic HMG-CoA reductase inhibitors. It also discloses that, in the following structural formula (hereinafter referred to as "Exhibit Ko 16, structural formula") "



2: A–B = (*E*)-CH=CH
3: A–B = (*Z*)-CH=CH
4: A–B = CH_2CH_2

CH for the numbers 2a to 2q of Y=Table II, N for the numbers 2t to 2w),"

the substitution at the 2-, 4-, and 6-positions (R^1, R^2, and R^3) of the central aromatic ring (pyrimidine ring) results in strong biological activity, and that the introduction of an isopropyl group at the 2-position (R^1) may maximize the biological activity, and that an analogous structure at the 4-position (R^2) of 4-chlorophenyl and 4-fluorophenyl substitutions may become a comparably strong inhibitor, and that the substitution at the 6-position (R^3) is the most important for the optimal biological activity, and the introduction of a bulky alkyl group or a phenyl moiety may achieve a significant increase of titer.

Here, although the compound of the Exhibit Ko 1 Invention is not a lactone body of dihydroxyheptenoic acid, but a sodium salt of dihydroxyheptenoic acid, it corresponds to one where "2:A-B=(E)-CH=CH" and the isopropyl group is introduced into R^1, and R^2 is substituted with 4-fluorophenyl in the structural formula of Exhibit Ko 16. Therefore, a person ordinarily skilled in the art who read Exhibit Ko 16 would recognize that the introduction of a bulky, lipophilic substituent group, in particular a bulky alkyl group or phenyl moiety into a moiety of "dimethylamino group" at the 2-position of the pyrimidine ring of the compound of Exhibit Ko 1 Invention corresponding to R^3 in the structural formula of Exhibit Ko 16 would probably result in a significant increase of titer.

Consequently, even if there was a motivation to select a more hydrophilic compound having an HMG-CoA reductase inhibiting activity in view of the side

effects as of the priority date, whereas a person ordinarily skilled in the art would recognize that the introduction of a bulky, lipophilic substituent group, in particular a bulky alkyl group or phenyl moiety into a moiety of "dimethylamino group" at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention would probably result in a significant increase of titer. Therefore, it cannot be said that there was a motivation for a person ordinarily skilled in the art as of the priority date to replace "dimethylamino group" at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a more hydrophilic substituent group, and not a bulky, lipophilic substituent group.

(d) Further, Exhibit Ko 9 and Ko 60 describe a number of groups other than methylsulfonyl group ($-SO_2CH_3$) as a group more hydrophilic than a methyl group. Even if there was a motivation for a person ordinarily skilled in the art as of the priority date to replace the dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a more hydrophilic substituent group, it cannot be said from the common general technical knowledge as of the priority date that there was a motivation for a person ordinarily skilled in the art to replace one of the methyl groups with a specific methylsulfonyl group as of the priority date.

Further, for a similar reason to the fact that there is no motivation to replace one methyl group of the dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with a methylsulfonyl group, there is no motivation to replace one methyl group of the dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with an alkylsulfonyl group (ethylsulfonyl group, propylsulfonyl group etc.) other than a methylsulfonyl group.

(e) Therefore, it cannot be said that there was a motivation to replace the dimethylamino group at the 2-position of the pyrimidine ring of the compound of the Exhibit Ko 1 Invention with "$-N(CH_3)(SO_2R')$" even if Exhibit Ko 2 might be evaluated as describing the structure according to the difference (1-i). It cannot be said that there was a motivation to adopt the structure of the difference (1-i) in the Exhibit Ko 1 Invention.

(E) Further, Plaintiffs argue that, in the determination of the support requirement, the trial decision determined by formulating a problem to provide a

compound having "excellent HMG-CoA reductase inhibiting activity" to the extent that the compound may become a pharmaceutical product capable of "suppressing the production of cholesterols" or an HMG-CoA reductase inhibitor including the compound as an active ingredient, whereas in the determination of the inventive step, it determined by formulating a criterion "to maintain a current level of HMG-CoA reductase inhibiting activity of the compound of Exhibit Ko 1 Invention," which goes beyond a level required by the problem to provide a pharmaceutical product capable of "suppressing the production of cholesterols." Thus it is not reasonable to determine support requirement and motivation with such a double standard.

The above determination of the support requirement in the trial decision among the above argument is correct as described in the following item 4. In contrast, regarding the inventive step, as is already determined, Exhibit Ko 2 fails to describe the structure according to the difference (1-i). Further, even if Exhibit Ko 2 might be evaluated as describing the structure according to the difference (1-i), it cannot be said that there was a motivation to adopt the structure according to the difference (1-i), and thus the Invention was not easily conceivable. The inventive step was not determined with a criterion as Plaintiffs argue. Thus no discrepancy is caused as Plaintiffs argue.

(F) As seen above, it cannot be said that it was possible to adopt the structure of the difference (1-i) in the Exhibit Ko 1 Invention.

B Summary

Consequently, without considering the difference (1-ii), it cannot be recognized that Invention 1 was easily conceivable by a person ordinarily skilled in the art by combining the Exhibit Ko 1 Invention and the Exhibit Ko 2 Invention.

Further, the compounds of Inventions 2, 5, and 9 to 11 are encompassed in Invention 1, whereas Invention 1 was not easily conceivable by a person ordinarily skilled in the art. Therefore, it cannot be said that Inventions 2, 5, and 9 to 11 with further limitation to the Invention 1 were also easily conceivable by a person ordinarily skilled in the art.

Further, the HMG-CoA reductase inhibitor of Invention 12 is an HMG-CoA reductase inhibitor including the compound of the Invention 1 as an active ingredient, whereas Invention 1 was not easily conceivable by a person ordinarily skilled in the art. Therefore, it cannot be said that Invention 12 was also easily conceivable by a person ordinarily skilled in the art.

Therefore, it cannot be recognized that Inventions 1, 2, 5, and 9 to 12 were

easily conceivable by combining both the Exhibit Ko 1 Invention and the Exhibit Ko 2 Invention. The ground 1 for rescission presented by Plaintiffs is groundless.

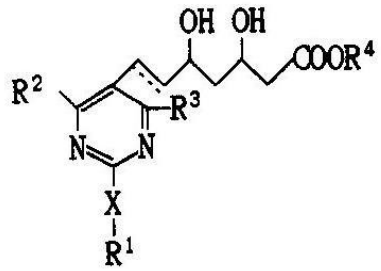
4 Ground 2 for rescission

(1) Determination criteria

The determination of whether or not the recitation of the scope of claims might conform to the support requirement should follow the steps of: comparing the recitation of the scope of claims with the description of the Detailed Descriptions of the Invention; and considering whether or not the Invention recited in the scope of claims might be the invention described in the Detailed Description of the Invention and fall within the range in which a person ordinarily skilled in the art could recognize that the problem to be solved by the Invention might be solved, or considering whether or not the Invention recited in the scope of claims might fall within the range in which a person ordinarily skilled in the art could recognize without the explicit description or suggestion in view of the common general technical knowledge as of the filing that the problem to be solved by the Invention might be solved (see the judgment of IP High Court, Special Division, made on November 11, 2005 for 2005 (Gyo-Ke) 10042).

(2) Problem to be solved by the Invention

A As seen in the aforesaid item 2(1)C and D, the description discloses in paragraph [0003] that "the suppression of cholesterol production is essential for the prevention and the treatment of atherosclerosis. Taking this into consideration, there is still a need for the development of useful pharmaceutical products.", and in paragraph [0004] that, in view of such circumstances, the inventors have completed the Invention "on the basis of the findings that the compound represented by the following general formula (I):



(wherein R_1 is a lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; each of R^2 and R^3 is independently hydrogen, a lower alkyl, or aryl, and each of said alkyl and aryl may have one or more substituents; R_4 is hydrogen, a lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is

sulfur, oxygen, or a sulfonyl group, or imino which may have a substituent; the dashed line represents the presence or absence of a double bond) has excellent HMG-CoA reductase inhibiting activity." The compound represented by this general formula (I) encompasses the compounds of Inventions 1, 2, 5, and 9 to 11, and Invention 12 is directed to an HMG-CoA reductase inhibitor including the compound of the Invention 1 as an active ingredient. Therefore, the problem to be solved by Inventions 1, 2, 5, and 9 to 11 lies in the provision of the compound having excellent HMG-CoA reductase inhibiting activity, and the problem to be solved by Invention 12 lies in the provision of an HMG-CoA reductase inhibitor including such compounds.

B As in the aforesaid 2(1)B, the specification discloses in paragraph [0002] that there were first generation HMG-CoA reductase inhibitors such as Mevinolin, which were obtained from fungal metabolites or their partial modified compounds, while synthesized HMG-CoA reductase inhibitors such as Pravastatin have been developed and expected as the second generation.

However, the Detailed Description of the Invention of the specification does not disclose any problem of these HMG-CoA reductase inhibitors that have already been developed. As seen in the aforesaid item 2(1)C, it only discloses in paragraph [0003] that "the suppression of cholesterol production is essential for the prevention and the treatment of atherosclerosis. Taking this into consideration, there is still a need for the development of useful pharmaceutical products."

According to the evidence (Exhibit Ko 36) and the entire import of the oral argument, although the pharmacological activity of a new active ingredient is at the same level as an active ingredient that has been commercially available in the field of pharmaceutical products, the new active ingredient has a technical value in that it provides an alternative means for solution.

Taking the above into consideration, it cannot be said that a problem to be solved by the Invention is to provide an HMG-CoA reductase inhibitor superior to the above HMG-CoA reductase inhibitors that have already been developed.

C Therefore, the problem to be solved by the Invention should be to provide a compound having excellent HMG-CoA reductase inhibiting activity to the extent that the compound may become a pharmaceutical product for suppressing the production of cholesterols, and to provide an HMG-CoA reductase inhibitor including the compound as an active ingredient.

(3) Means for solution

A As in the aforesaid item 2(1)E, the specification discloses a specific procedure of measuring HMG-CoA reductase inhibiting activity by use of rat liver microsome fraction in paragraphs [0040] and [0041], and in paragraph [0042] that the HMG-CoA reductase inhibiting activity of compound (Ia-1) is 442 given the HMG-CoA reductase inhibiting activity of sodium Mevinolin be 100 as a measurement result.

This compound (Ia-1) is "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid sodium salt" (the specification [0029]). It is not "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid," nor its " hemicalcium salt," which are encompassed in Invention 1. Therefore, it is not encompassed in Invention 1; however, according to the entire import of the oral argument, it is recognized that the difference of salt does not greatly affect HMG-CoA reductase inhibiting activity. Compound (Ia-1) and the compound of Invention 1 have a comparable level of HMG-CoA reductase inhibiting activity. Therefore, supposing that compound (Ia-1) has a higher level of HMG-CoA reductase inhibiting activity compared to sodium Mevinolin, it can be said that a person ordinarily skilled in the art would understand that "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" and its " hemicalcium salt" might also have a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin.

Although the above measurement result is a result of one-time measurement, it does not influence the above determination, nor is there other evidence sufficient to find circumstances which question the reliability of the above determination.

Further, Invention 1 includes a compound of formula (I) where R^1 is a lower alkyl, R^2 is a phenyl substituted with halogen, R^3 is a lower alkyl, and X is an imino group substituted with an alkylsulfonyl group. These substituent groups have analogous chemical structure to the group of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" and the group of its "hemicalcium salt" (where R^1 is a methyl, R^2 is a phenyl substituted with fluorine, R^3 is an isopropyl, X is an imino group substituted with a methylsulfonyl group). Therefore, it can be said that a person ordinarily skilled in the art would understand that the remaining compounds included in Invention 1 might also have a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin, like the compound (Ia-1), or "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-

(3R,5S)-dihydroxy-(E)-6-heptenoic acid" and its "hemicalcium salt." There is no evidence against this fact.

Consequently, it can be said that the Detailed Description of the Invention of the specification discloses to the extent that allows a person ordinarily skilled in the art to recognize that the compound of Invention 1 has an excellent HMG-CoA reductase inhibiting activity to provide a pharmaceutical product suppressing the production of cholesterols; i.e., the compound can solve the problem to be solved by the Invention.

B Further, the compounds of Inventions 2, 5, and 9 to 11 are encompassed in the Invention 1, and the HMG-CoA reductase inhibitor of Invention 12 is an HMG-CoA reductase inhibitor including the compound of Invention 1 as an active ingredient. Similarly, it can be said that the Detailed Description of the Invention of the specification discloses to the extent that allows a person ordinarily skilled in the art to recognize that the Invention can solve the problem to be solved by the Invention.

(4) The argument by Plaintiffs

A(A) Plaintiffs argue that the HMG-CoA reductase inhibitor of Compactin had been publicly known more than a decade before the filing, and a plurality of HMG-CoA reductase inhibitors were already commercially available as of the filing, the compound showing a stronger HMG-CoA reductase inhibiting activity compared to sodium Mevinolin was also publicly known, and thus "to the extent that the compound might become a pharmaceutical product for suppressing the biosynthesis of cholesterols" is inappropriate since it is a level lower than the common general technical knowledge.

As discussed in the aforesaid item (2), however, it cannot be said that a problem to be solved by the Invention is to provide a compound or a drug with an HMG-CoA reductase inhibiting activity superior to the HMG-CoA reductase inhibitors that have been already developed.

Therefore, the above argument presented by Plaintiffs is not acceptable due to the erroneous premise.

(B) Plaintiffs argue that Invention 1 is encompassed in the scope of general formula (I) of Exhibit Ko 2, and thus the significant effects are necessary in comparison to the other compounds of general formula (I) of Exhibit Ko 2 in order to be affirmed the inventive step, whereas a degree of "to the extent that the compound might become a pharmaceutical product for suppressing the biosynthesis of

cholesterols" is inappropriate, since it is such a level lower than the common general technical knowledge as of the filing that could not involve the inventive step as a selection invention.

However, the support requirement is specified as a requirement for the recitation of the scope of claims to prevent the establishment of an exclusive right for an invention not disclosed by reciting an invention not described in the Detailed Description of the Invention in the scope of claims (Article 36, paragraph (5), item (i) of the Patent Act before the revision by Heisei 6 Act No. 116), whereas the inventive step is specified as a patent requirement to eliminate an invention easily conceivable by a person ordinarily skilled in the art as of the filing on the basis of a publicly known technique from a target of the grant of a patent to prevent a grant of an exclusive right for such an invention (Article 29, paragraph (2) of the Patent Act). Consequently, the determination of whether or not to conform to the support requirement should be made from the above viewpoint, and the determination of the inventive step should not be encompassed into the framework.

Therefore, the above argument presented by Plaintiffs is not acceptable.

(C) Plaintiffs argue that the applicant recognized that the compound of Invention 1 and the Exhibit Ko 1 Invention falls within a range of the general formula (I) of Exhibit Ko 2, and thus could not formulate a problem to be solved to provide a HMG-CoA reductase inhibitor including a compound having an excellent HMG-CoA reductase inhibiting activity or the compound as an active ingredient "to the extent that the compound might become a pharmaceutical product for suppressing the biosynthesis of cholesterols."

The determination of the support requirement should be made, however, with respect to the recitation of the scope of claims and the description of the Detailed Description of the Invention in view of the common general technical knowledge as of the filing. It cannot be construed that the determination varies depending on the Applicant's subjective view as of the filing.

Therefore, the above argument presented by Plaintiffs is not acceptable.

B(A) Plaintiffs argue that the Detailed Description of the Invention of the specification fails to show the significant HMG-CoA reductase inhibiting activity of the Invention, and thus a person ordinarily skilled in the art could not recognize that "the problem to be solved by the Invention" might be solved.

As in the aforesaid item (2), however, the problem to be solved by the Invention

should be to provide a compound having excellent HMG-CoA reductase inhibiting activity to the extent that the compound may become a pharmaceutical product for suppressing the biosynthesis of cholesterols, and to provide an HMG-CoA reductase inhibitor including the compound as an active ingredient. It can be said that the Detailed Description of the Invention of the specification discloses to the extent that allows a person ordinarily skilled in the art to recognize that this problem can be solved. The above argument by Plaintiffs is premised on the fact that the Invention needs to have a "significant" HMG-CoA reductase inhibiting activity. But such argument is based on an incorrect premise, and thus is not acceptable.

(B) Plaintiffs argue that the compound of the Invention is a selection invention of general formula (I) of Exhibit Ko 2, and thus no new technique is disclosed by specifying a structure without the disclosure of significant activity.

However, the determination of whether or not to conform to the support requirement should be made independent of the determination of the inventive step, as in the aforesaid item A(B).

Therefore, the above argument presented by Plaintiffs is not acceptable due to the erroneous premise.

(C) Plaintiffs argue that the Patentee had admitted in the trial that Invention 1 was not supported by data of the compound (Ia-1) described in the Detailed Description of the Invention of the specification, and thus a person ordinarily skilled in the art could not recognize that the problem might be solved by Invention 1.

The determination of the support requirement should be made, however, with respect to the recitation of the scope of claims and the description of the Detailed Description of the Invention in view of the common general technical knowledge as of the filing. It cannot be construed that the determination varies depending on the Patentee's argument in the trial stage.

Therefore, the above argument presented by Plaintiffs is not acceptable.

C Plaintiffs argue that, even if compound Ia-1 of the Detailed Description of the Invention of the specification has an HMG-CoA reductase inhibiting activity higher than that of sodium Mevinolin, since Exhibit Ko 16 suggests that the HMG-CoA reductase inhibiting activity decreases by a factor of 100 times or more by substituting an isopropyl group corresponding to R^3 of the formula (I) of the Invention 1 in compound Ia-1 with a methyl group, it cannot be recognized that a person

ordinarily skilled in the art could understand that the overall range of compounds of the Invention 1 has a higher HMG-CoA reductase inhibiting activity compared to sodium Mevinolin, like compound Ia-1.

Indeed, there is a large difference in HMG-CoA reductase inhibiting activity between compound 2t and compound 2r or 2s among the compounds of Exhibit Ko 16, the moiety corresponding to R^3 of formula (I) of Invention 1 is an isopropyl group for 2t, whereas it is a methyl group for 2r and 2s. In addition to the above, however, 2t, and 2r or 2s of Exhibit Ko 16 are different from each other in that the moiety corresponding to "-X-R^1" of formula (I) of the Invention 1 is an isopropyl group for 2t, whereas it is a methyl group for 2r and 2s. As for this difference, Plaintiffs argue that HMG-CoA reductase inhibiting activity may be reduced by at most a factor of three times as a result of the comparison between the compounds of pyrimidine ring skeleton, 2f and 2e, of Exhibit Ko 16. Exhibit Ko 16 only discloses that "In general, the structure-activity relationship of pyrimidine (2r-w) is comparable to the structure-activity relationship of pyridines (2a-q) (e.g. 2i vs. 2v, 2a vs. 2r, 2j vs. 2w; Table 1)." Exhibit Ko 16 may not be evaluated as describing that the effect of the difference in a structure other than a ring structure on the HMG-CoA reductase inhibiting activity is comparable between a compound with a pyridine ring skeleton and a compound with a pyrimidine ring skeleton. Therefore, it cannot be said that, regarding the compounds with pyrimidine ring skeleton of the compound 2t and the compounds 2r and 2s of Exhibit Ko 16, the effect of the difference in a moiety corresponding to "-X-R^1" of formula (I) of the Invention 1 on the HMG-CoA reductase inhibiting activity is a factor of about 3 times. Furthermore, compound Ia-1 has alkylsulfonyl group at a moiety corresponding to "-X-R^1" of formula (I) of Invention 1, which differs from the above 2t, 2r, and 2s.

Consequently, it is insufficient to find the common general technical knowledge of a person ordinarily skilled in the art as of the filing from only Exhibit Ko 16 that the HMG-CoA reductase inhibiting activity decreases by a factor of 100 times or more by substituting an isopropyl group corresponding to R^3 of formula (I) of the Invention in compound Ia-1 with a methyl group.

Therefore, the above argument presented by Plaintiffs is not acceptable.

(5) Summary

As seen above, it cannot be said that the Inventions 1, 2, 5, and 9 to 12 do not comply with the provisions of Article 36, paragraph (5), item (i) of the Patent Act prior

to amendment by Act No.116 of 1994, of which the provisions then in force shall remain applicable according to revision supplement Article 6, paragraph (2) of Act No. 116 of 1994.

Therefore, none of the ground 2 for rescission presented by Plaintiffs is reasonable.

No. 8 Conclusion

Accordingly, none of the argument of the ground for rescission presented by Plaintiffs is reasonable.

Therefore, all the Plaintiffs' claims shall be dismissed, and the court renders as in the main text.

Intellectual Property High Court, Special Division

Chief Judge _____
Misao SHIMIZU

Judge _____
Makiko TAKABE

Judge _____
Yoshiyuki MORI

Judge _____
Toshihiko TSURUOKA

Judge _____
Ayako MORIOKA