Trial decision

Invalidation No. 2015-800095

Ibaraki, Japan
Demandant HIBINO, Kenichi

Kanagawa, Japan
Patent Attorney TSUJITA, Tomoko

Kanagawa, Japan
Patent Attorney MURAMATSU, Daisuke

Tokyo, Japan
Intervenor NIPPON CHEMIPHAR CO. LTD.

Kanagawa, Japan
Patent Attorney TSUJITA, Tomoko

Kanagawa, Japan
Patent Attorney MURAMATSU, Daisuke

Osaka, Japan
Demandee SHIONOGI & CO. LTD.

Tokyo, Japan
Attorney ONO, Seiji

Tokyo, Japan
Patent Attorney MATSUTOYA, Yuko

Tokyo, Japan
Attorney KANEMOTO, Keiko

Tokyo, Japan
Patent Attorney UMEDA, Shinsuke

UK
Intervenor ASTRAZENECA UK LTD.

Tokyo, Japan
Patent Attorney TERACHI, Takumi

Tokyo, Japan
Attorney SUEYOSHI, Tsuyoshi

The case of trial regarding the invalidation of Japanese Patent No. 2648897, entitled "Pyrimidine Derivative" between the parties above has resulted in the following trial decision:

Conclusion

The demand for trial of the case was groundless.

The costs in connection with the trial shall be borne by the demandant.

Reason

No. 1 History of the procedures

The present application relating to an invention entitled "Pyrimidine Derivative" was filed as Patent Application No. H4-164009 on May 28, 1992 (internal priority claim: July 1, 1991) by SHIONOGI & CO., LTD. as an applicant (hereinafter referred to as the "demandee"), and the establishment of patent right was registered on May 16, 1997 as Japanese Patent No. 2648897 (12 claims) (hereinafter the patent is referred to as the "Patent", and the description is referred to as the "Description of the Patent".)

Then, a trial for invalidation (invalidation No. 2014-80002, hereinafter referred to as the "earlier invalidation trial) was demanded by another demandant than the demandant of the invalidation trial of the case. Then, the trial decision dated June 29, 2015 was delivered to the effect that the correction should be approved as request, the demand for trial of the case was groundless, and the costs in connection with the trial should be borne by the demandant. As a result, the correction to cancel claims 3, 4, 7 and 8 was established. Although a lawsuit against the trial decision was filed on July 29, 2015, the lawsuit was withdrawn. Therefore, the trial decision became final and

binding on July 29, 2015, and corrections relating to claims 1, 2, 5, 6, and 9 to 17 were also finally approved as described in a request for correction.

Next, the trial for invalidation of the case was demanded by Kenichi Hibino (hereinafter referred to as the "demandant"), and the history of the procedures is as follows:

March 31, 2015	Submission of a written demand for trial/Evidence A No. 1 to A No. 32 (demandant)
May 22, 2015	Written amendment (demandant)
June 5, 2015	Written statement (demandee)
August 3, 2015	Submission of a written reply for the trial case/ Evidence B No. 1 to B No.55 (demandee)
	Request for a correction
September 18, 2015	Written amendment (demandee)
October 2, 2015	Written statement (demandee)
October 29, 2015	Application for intervention from ASTRAZENECA UK LIMITED (hereinafter referred to as the "supporting intervener")
	Same dayWritten statement/ Evidence B No. 1 to B No. 7 (intervener)
November 4, 2015	Submission of a written refutation of a trial case/Evidence A No. 33 to A No. 52 (demandant)
November 11, 2015	Written opinion (demandant)
	Written amendment (demandant)
December 11, 2015	Decision on intervention (Permission for the Application for intervention)
December 16, 2015	Notice of reasons for refusal of correction/A notice of a result of proceeding by ex officio
December 25, 2015	Written opinion (demandant)
January 18, 2016	Written statement (demandee)
February 8, 2016	Notification of trial examination
March 24, 2016	Submission of a written statement/Evidence A No. 8 to A No. 2, Evidence A No. 53 to A No. 55 (demandant)
	Submission of a written statement/Evidence B No. 56 to B No. 61 (demandee)

	Written statement/Evidence B No. 8 to B No. 11 (supporting intervener)
April 7, 2016	Oral proceedings statement brief (demandant)
	Submission of An oral proceedings statement brief/Evidence B No. 62 (demandee)
	Submission of An oral proceedings statement brief/Evidence B No. 12 (supporting intervener)
April 15, 2016	Written statement/Evidence B No. 13 (supporting intervener)
April 21, 2016	Oral proceedings
	Decision on acceptance or nonacceptance of amendment
April 22, 2016	Resubmission of a written statement/Evidence A No. 43 (demandant)
May 6, 2016	Application for intervention from NIPPON CHEMIPHAR CO., LTD. (hereinafter referred to as the "main intervenor")
June 9, 2016	Decision on intervention (Permission for the Application for intervention)
June 21, 2016	Notice of conclusion of trial proceedings

No. 2 Judgment by the Body on Propriety of Correction

The demandee submitted a request for a correction on August 3, 2015 that fell within a time frame designated by the chief administrative judge to request for correction that is specified in Article 134 (1) of the Patent Act, and requested to correct the description and scope of claims of the case on the basis of every claim or each group of claims as described in the corrected description and scope of claims attached to the request for a correction (hereinafter referred to as the "correction of the case").

Since the trial decision of the earlier invalidation trial became final and binding in the Patent as described above in "Reason No. 1", the establishment of the patent right is considered to be registered by the corrected description and scope of claims that were claimed in the earlier invalidation trial under the provisions of Article 128 of the Patent Act which is applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

As indicated in the above-described notice of reasons for refusal of correction, the content of the correction of the case is identical to the corrected description and scope of claims that were already made in the earlier invalidation trial.

Consequently, no correction is to be made in accordance with the correction of the case.

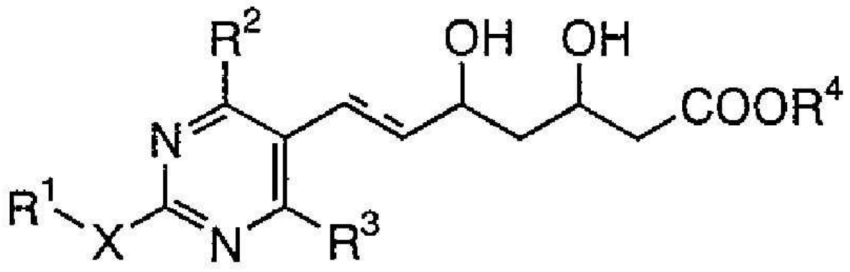
Therefore, the correction of the case is not intended for the matters listed in any

of the items of Article 134-2(1) of the Patent Act, and thus, the correction of the case shall not be approved.

No. 3 The Invention

Since the correction of the case shall not be approved as described above in "Reason No. 2", the inventions relating to claims 1, 2, 5, and 9 to 12 (hereinafter referred to as "Invention 1", "Invention 2", "Invention 5", and "Invention 9" to "Invention 12", and collectively as "the Inventions") are recognized as the claims 1, 2, 5, and 9 to 12 in the scope of claims after the correction that were made in the earlier invalidation trial.

[Claim 1] A compound comprising one of a compound and its lactone ring closure compound expressed by formula (I):
[Chemical formula 1]



(where
R^1 represents a low-grade alkyl;
R^2 represents phenyl substituted with a halogen;
R^3 represents a low-grade alkyl;
R^4 represents a calcium ion that forms one of a hydrogen salt and a hemicalcium salt;
X represents an imino group replaced with an alkylsulfonyl group; and
broken lines indicate presence or absence of a double bond).

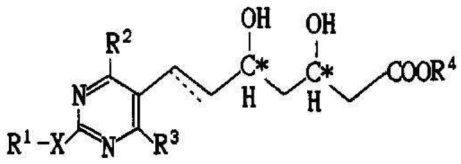
[Claim 2] A (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl] (3R, 5S)-dihydroxy-(E)-6-heptenoic acid

[Claim 5] A compound expressed by formula (I):

[Chemical formula 2]
(Being the same as formula (I) in claim 1, the chemical formula is omitted.)
(where
R^1 represents a low-grade alkyl;
R^2 represents a phenyl substituted with a halogen;
R^3 represents a low-grade alkyl;
R^4 represents a calcium ion that forms a hemicalcium salt;
X represents an imino group substituted with a methylsulfonic group; and
broken lines indicate presence or absence of a double bond).

[Claim 9] A compound expressed by formula (I):
[Chemical formula 4]
(Being the same as the formula (I) in claim 1, the chemical formula is omitted.)
(where
R^1 represents a low-grade alkyl;
R^2 represents a phenyl substituted with a halogen;
R^3 represents a low-grade alkyl;
R^4 represents a calcium ion that forms a hemicalcium salt;
X represents an imino group substituted with a methylsulfonic group; and
broken lines indicate presence or absence of a double bond).

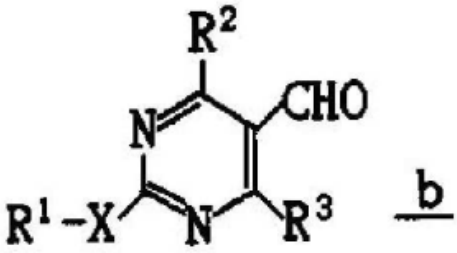
[Claim 10] An optically active substance expressed by formula (I):
[Chemical formula 8]



(I)

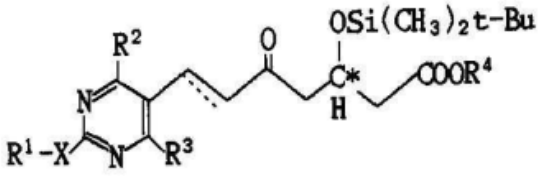
,

formula (I) being obtained by a method comprising the steps of:
reacting a compound expressed by formula (b) with a (3R)-3-(tert-butyldimethylsilyloxy-5-oxo-6-triphenyl phosphoranyliden hexanoic acid derivative to produce a compound expressed by formula (c);
[Chemical formula 5]



b

[Chemical formula 6]

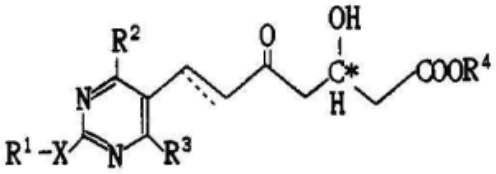


c

,

producing a compound expressed by formula (d) by separating the tert-butyldimethylsilyl group from the compound expressed by formula (c);

[Chemical formula 7]



d

and

reducing the compound expressed by formula (d),

(where

R^1 represents a low-grade alkyl;

R^2 represents a phenyl substituted with a halogen;

R^3 represents a low-grade alkyl;

R^4 represents a calcium ion that forms a hemicalcium salt;

X represents an imino group substituted with an alkylsulfonyl group;

broken lines indicate presence or absence of a double bond;

t-Bu represents tert-butyl; and

C* represents an asymmetric carbon atom).

[Claim 11] A calcium salt of

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

[Claim 12] An HMG-CoA reductase inhibitor comprising the compound according to claim 1 as an active ingredient.

No. 4 Object of the Demand, and Outline of the Allegation, Evidences Submitted by the Demandant, and Main Intervenor's Allegation

1. The Gist of Reasons for Invalidation Described in the Written Demand for Trial, the Written Refutation in the Trial Case, the Oral Proceedings Statement Brief, and the Written Statement

The object of the demand alleged by the demandant is acknowledged as follows; "the body is requested to approve that the patent relating to the inventions according to claims 1, 2, 5, and 9 to 12 of Patent No. 2648897 is invalidated, and the costs in connection with the trial shall be borne by the demandee" (see the written demand for trial, p. 1, "6. The Object of the Demand", the written refutation of the trial case, p. 2 "7. Reason", "7-1"(1) and (2), and the 1st oral proceedings record, "demandant 1").

The gist of the reasons for invalidation alleged by the demandant is as follows (see the written demand for trial, p. 2, l. 2 to p. 5, l. 8, p. 53, l. 19 to p. 69, l. 15, the written Amendment dated May 22, 2015 "6. Details of amendment", the written refutation of the trial case, p. 2, "7. Reason", "7-1" (1) and (2), p. 24, 11th line from the bottom to p. 50, l. 15, the Notification of trial examination, "13th (1) and (2)", the written statement dated March 24, 2016, p. 16, 8th line from the bottom to p. 29, l. 20, the oral proceedings statement brief, p. 2, 5th line from the bottom to p. 27, the last line, and the 1st oral proceedings record, "demandant 2").

(1) Reason 1 for invalidation

The Inventions 1, 2, 5, and 9 to 12 could have been easily conceived of by a person ordinarily skilled in the art before the priority date for the Invention according to the inventions described in Evidence A No. 1 (the main Cited Document) and Evidence A No. 2a distributed in Japan or abroad before the priority date for the Invention, and the common general technical knowledge at the time of the priority date for the Invention, and thus, the demandee should not be granted a patent for the Inventions 1, 2, 5, and 9 to 12 in accordance with the provisions of Article 29(2) of the Patent Act.

Therefore, since the patent for the Inventions 1, 2, 5, and 9 to 12 violates the provisions of Article 29 of the Patent Act, it falls under Article 123(1) (ii), and should be invalidated.

(2) Reason 2 for invalidation

Since compared with the prior art, the Inventions 1, 2, 5, and 9 to 12 cannot be said to be notably active, a person skilled in the art cannot understand that the Inventions can solve the problems to be solved that are described in the detailed description. Thus, the invention for which a patent is sought described in the scope of claims cannot be said to be described in the detailed description of the invention.

Therefore, the description of the scope of claims for the Patent does not comply with Article 36(5)(i) of the Patent Act before revision by the Act No. 116 of 1994, of which the provisions then in force shall remain applicable according to revision supplement Article 3(1) of the Act No. 116 of 1994 (hereinafter referred to as the "Patent Act before revision of 1994", so that the patent for the Inventions 1, 2, 5, and 9 to 12 is granted for a patent application that does not meet the requirement stipulated in Article 36(5) of the Patent Act, and falls under Article 123(1)(iv) and should be invalidated.

(3) Decision on acceptance or nonacceptance of amendment

A decision on acceptance or nonacceptance of amendment about the amendment of the statement of the demand that the demandant made in the written refutation of the trial case was made in accordance with Article 131(2)(ii) of the Patent Act (see the 1st oral proceedings record, "Chief administrative judge 2").

A Since the amendment to invalidate the patent relating to claims 13, and 15 to 17 is to change the gist of the demand and the demandee does not agree with the amendment, it is not allowed.

B Since the amendment to add reasons 3 to 5 for invalidation is to change the gist of the demand and the demandee does not agree with the amendment, it is not allowed.

2. Evidences Submitted by the Demandant

The evidences submitted by the demandant are as follows.

(1) The evidences submitted in the written demand for trial and the written amendment dated May 22, 2015

Evidence A No. 1, National Publication of International Patent Application No. H03-501613

Evidence A No. 2, Japanese unexamined patent application publication No. H01-261377

Evidence A No. 3, An internal document by the patentee of the present case entitled "Managerial challenge report"

(DTX-72), August 26, 1996,

(Evidence A No. 3 in the earlier invalidation trial)

Evidence A No. 4, a document from Mr. Adrian G. Flinn to Mr. Yamaguchi of SHIONOGI & CO., LTD. (DTX-175), December 17, 1997

(Evidence A No. 4 in the earlier invalidation trial)

Evidence A No. 5, an internal document of the patentee of the present case entitled "Past Q & A with ZENECA about S-4522 Patent" (PTX-0950), January 30, 1998

(Evidence A No. 5 in the earlier invalidation trial)

Evidence A No. 6, a written opinion dated August 12, 1996 relating to the patent application of the Patent

Evidence A No. 7, Bruce D. Roth, et al., *Journal of Medicinal Chemistry*, Vol. 34, No. 1, 1991 Jan., pp. 463 to 466

Evidence A No. 8, F. G. Kathawala, *Medicinal Research Reviews*, Vol. 11, No. 2, 1991 Mar., pp.121 to 146

Evidence A No. 9, SASAKI, Tadashi, *Action Molecule Design, Drug Design for synthetic chemists*, NANKODO CO., LTD., May 1, 1974, the front cover, pp. 123 to 136, and the copyright page

Evidence A No. 10, *Life Science Basic Biochemistry,* translated by KOMANO, Tohru, et al., KAGAKU-DOJIN PUBLISHING COMPANY, INC, April 1, 1987, the front cover, pp. 254 to 256, and the copyright page

Evidence A No. 11, *SEIKAGAKUJITEN*, TOKYO KAGAKU-DOJIN, PUBLISHING COMPANY, INC, April 10, 1984, edited by IMAHORI, Kazutomo, et al., the front cover, pp. 489 to 490, and p. 1010

Evidence A No. 12, Stephen M. Berge et al., *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, 1977, pp. 1 to 19

Evidence A No. 13, Philip L. Gould, *International Journal of Pharmaceutics*, Vol. 33, 1986, pp. 201 to 217

Evidence A No. 14, Scott M. Grundy, *The New England Journal of Medicine*, Vol. 319, No. 1, 1988 pp. 24 to 33,

Evidence A No. 15, S. Y. Sit et al., *Journal of Medicinal Chemistry*, Vol. 33, No. 11, 1990, pp. 2982 to 2999

Evidence A No. 16, G. Beck et al., *Journal of Medicinal Chemistry*, Vol. 33, No. 1, 1990, pp. 52 to 60

Evidence A No. 17, TSUJITA, Yoshio, et. al, *Biochimica et Biophysica Acta*, Vol. 877,

1986, pp. 50 to 60,

Evidence A No. 18, N. Balasubramanian et. al, *Journal of Medicinal Chemistry*, Vol. 32, No. 9, 1989**,** pp. 2038 to 2041

Evidence A No. 19, Rex. A. Parker, et. al, *Journal of Lipid Research,* Vol. 31, 1990, pp. 1271 to 1282

Evidence A No. 20, WATANABE, Hidetoshi, *Sankyo Kenkyusho Nempo*, Vol. 42, 1990, pp. 117 to 120

Evidence A No. 21, Abu T. M. Serajuddin, et. al, *Journal of Pharmaceutical Sciences*, Vol. 80, No. 9, 1991, pp. 830 to 834

Evidence A No. 22, IDE, Hajime, et al., *Doumyakukoka*, Vol. 15, No. 1, 1987, pp. 83 to 89

Evidence A No. 23, FUJII, Setsuro, et al., *Doumyakukoka*, Vol. 13, No. 2, 1985 pp. 251 to 258

Evidence A No. 24, Stephen T. Mosley, et al. *Journal of Lipid Research*, Vol. 30, 1989, pp. 1411 to 1420

Evidence A No. 25, SERIZAWA, Nobufusa, et al. *The Journal of Antibiotics*, Vol. XXXVI, No. 5, 1983, pp. 604 to 607

Evidence A No. 26, B. D. Roth, et al., *Journal of Medicinal Chemistry*, Vol. 33, No. 1, 1990, pp. 21 to 31

Evidence A No. 27, Japanese unexamined patent application publication No. H03-99075

Evidence A No. 28, WATANABE, Hidetoshi, et al., *Chemical and Pharmaceutical Bulletin*, Vol. 35, No. 4, 1987, pp. 1452 to 1459

Evidence A No. 29, "List of Pharmaceutical Development Articles Having a Methylsulfonyl Group", written by TSUJITA, Tomoko, March 30, 2015

Evidence A No. 30, Canadian Patent Office Record 1132610

Evidence A No. 31, a written opinion, September 17, 2014, written by Paul A. Grieco, (Evidence A No. 22 in the earlier invalidation trial)

Evidence A No. 32, a written opinion, September 20, 2014, written by Donna L. Romero, (Evidence A No. 23 in the earlier invalidation trial)

(2) The evidences submitted in the written refutation of the trial case

Evidence A No. 33, KISHIDA, Yukichi, et al., *Gekkan Yakuji,* Vol. 33, No. 6, June 1, 1991, the front cover, pp. 1099 to 1104, and the copyright page

Evidence A No. 34, KOMAI, Tohru, et al., *Doumyakukoka*, Vol. 18, No. 11, 1990, the front cover, the Table of Contents, p. 1007, and the copyright

page,

Evidence A No. 35, TSUJITA, Yoshio, *Doumyakukoka*, Vol. 18, No. 2, pp. 165 to 171, 1990

Evidence A No. 36, TSUJITA, Yoshio, *KAGAKU TO SEIBUTSU*, Vol. 28, No. 12, 1990 pp. 820 to 825

Evidence A No. 37, KOGA, Teiichiro, et al., *Biochimica et Biophysica Acta*, Vol. 1045, 1990, pp. 115 to 120

Evidence A No. 38, National Publication of International Patent Application No. H03-501492

Evidence A No. 39, Y. Tsujita, J. Drug Dev., Vol. 3 (suppl. 1), pp. 155 to 159

Evidence A No. 40, ENDOU, Akira, *Nippon Nogeikagaku Kaishi*, Vol. 65, No. 6, June 15, 1991, pp. 1019 to 1021

Evidence A No. 41, Japanese unexamined patent application publication No. H04-298508

Evidence A No. 42, KISHIDA, Yukichi, et al., *YAKUGAKU ZASSHI,* Vol. 111, No. 9, September 25, 1991, PP. 469 to 487

Evidence A No. 43, H. Jendralls, *Journal of Medicinal Chemistry*, Vol. 34, No. 10, 1991, pp. 2962 to 2983, received at University of Tsukuba Library on November 8, 1991

Evidence A No. 44-1, a description of European patent application No. 46484

Evidence A No. 44-2, Japanese unexamined patent application publication No. H04-352767

Evidence A No. 45-1, a description of European patent application No. 465265

Evidence A No. 45-2, Japanese unexamined patent application publication No. H04-230357

Evidence A No. 46-1, a description of European patent application No. 476493

Evidence A No. 46-2 Japanese unexamined patent application publication No. H07-2712

Evidence A No. 47, National Publication of International Patent Application No. H03-505729

Evidence A No. 48, a description of Japanese Patent Application No. 1991-188015

Evidence A No. 49, a description of U.S. reissue patent No. 37314

Evidence A No. 50, a patent filing, "Lactic Acid Bacterium For Animal Feed" by NH FOODS. LTD., "In-House Research Report", May 29, 2015

Evidence A No. 51, Japanese unexamined patent application publication No. S63-83053

Evidence A No. 52, Japanese unexamined patent application publication No.

(3) The evidences submitted in the written statement dated March 24, 2016

Evidence A No. 8-2, "Search Result Report", March 7, 2016, written by MATSUMURA, Daisuke,

Evidence A No. 33, resubmitted without the copyright page

Evidence A No. 36, resubmitted with the copyright page

Evidence A No. 40, resubmitted with the front cover

Evidence A No. 42, resubmitted with the front cover

Evidence A No. 53, *An Introduction to Practical Biochemistry*, Translated by HIROMI, Keitarou, et al., KAGAKU-DOJIN PUBLISHING COMPANY, INC, November 10, 1981, the front cover, pp. 1 to 13, and the copyright page,

Evidence A No. 54, F. G. Kathawala, *Trends in Medicinal Chemistry '88*, Vol. 12, 1989, pp. 709 to 728,

Evidence A No. 55, the determination 1997 (Gyo-Ke) 262

(4) The evidences submitted in the oral proceedings statement brief

Evidence A No. 56, *The Practice of Medicinal Chemistry*, Vol. 1, TECHNOMICS, INC., August 15, 1998, edited and translated by NAGASE, Hiroshi, the front cover, pp. 339, 343, 424 to 428, and the copyright page

Evidence A No. 57, *Iyakuhin Kaihatsu Gairon*, CHIJIN SHOKAN CO., LTD., December 1, 1970, edited by TSUDA, Kyosuke, et al., the front cover, pp. 66 and 67, and the copyright page

Evidence A No. 58, *Drug Design,* edited and translated by TAKAGI, Keijirou, HIROKAWA-SHOTEN LTD., December 10, 1977, the front cover, pp. 80 and 81, and the copyright page,

Evidence A No. 59, *Yakuhin Seizougaku*, edited by KAJI, Kenji, et al., NANKODO CO., LTD., April 20, 1984, the front cover, pp. 8 and 9, and the copyright page

Evidence A No. 60, *Yakubutsu-no Kouzoukasseisouka*n, edited by KOUZOUKASSEISOUKAN KONWAKAI, NANKODO CO., LTD., January 10, 1979, the front cover, pp. 84 and 85, and the copyright page

Evidence A No. 61, *Kouzoukasseisoukan and Drug Design*, edited by FUJITA, Norio, KAGAKU-DOJIN PUBLISHING COMPANY, INC, February

20, 1986, the front cover, pp. 4 to 7, and the copyright page

Evidence A No. 62, *Shinyaku-no Lead Generation*, edited by MORIGUCHI, Ikuo, et al., TOKYO KAGAKU-DOJIN, PUBLISHING COMPANY, INC, November 20, 1987, the front cover, pp. 20 and 21, and the copyright page

Evidence A No. 63, the determination 2009 (Gyo-Ke) 10238

(5) The evidences submitted in the written statement dated April 22, 2016

Evidence A No. 43, resubmitted with the front cover

3. Main Intervenor's Allegation

The main intervenor only states its intervention on behalf of the demandant in an application for intervention, and alleges nothing else.

No. 5 Object of the Reply, and Outline of the Allegation Thereof and Evidences Submitted by the Demandee

1. Outline of a reply described in a written reply for the trial case, an oral proceedings statement brief, and a written statement

The Object of the Reply alleged by the demandee is acknowledged as follows; "the body is requested to approve the correction as request, and approve that the demand for trial of the case was groundless, and the costs in connection with the trial shall be borne by the demandant" (see the written reply for the trial case, p. 2, "6 the object of the reply", and the 1st oral proceedings record, "demandee 1").

The demandee admits that the demandant alleges that neither of the above-described reasons 1 and 2 for invalidation alleged by the demandant has reasons in the written reply for the trial case, the written statement dated March 24, 2016, and the oral proceedings statement brief.

2. The Evidences Submitted by the Demandee

The evidences submitted by the demandee are as follows.

(1) The evidences submitted in the written reply for the trial case

Evidence B No. 1, Thomas A. Pearson, et al., *Arch. Intern. Med.*, Vol. 160, 2000, pp. 459 to 467

Evidence B No. 2, Michael H. Davidson, et al., *The American Journal of Cardiology*, Vol. 96, 2005, pp. 556 to 563

Evidence B No. 3, Thomas C. Andrews, et al., *The American Journal of Medicine*, Vol. 111, 2001, pp. 185 to 191

Evidence B No. 4, a written opinion, January 26, 2015, written by William R. Roush, (Evidence B No. 45 in the earlier invalidation trial)

Evidence B No. 5, Japanese unexamined patent application publication No. H01-294665

Evidence B No. 6, data of European patent application No. 330057, NRI Cyber Patent

Evidence B No. 7, a description of U.S. reissue patent No. 37314

Evidence B No. 8, United States District Court for the District of Delaware, Case 1:08-md -01949-JJF Document 555, June 29, 2010 (Infringement lawsuit initial court decision of the corresponding US patent of the patent)

Evidence B No. 9, Court of Appeals for the Federal Circuit, rosuvastatin calcium, patent suit court decision, December 14, 2012 (Infringement lawsuit appeal court decision of the corresponding US patent of the patent)

Evidence B No. 10, a description of European patent application No. 330057

Evidence B No. 11, R. Krause, J. Drug Dev., Vol. 3 (Suppl. 1), 1990, pp. 255 to 257

Evidence B No. 12, paper describing constitutional formulae and CLogP values of lovastatin and HR-780, June 4, 2014, written by MORIOKA, Hironori, (Evidence B No. 36 in the earlier invalidation trial)

Evidence B No. 13, Thomas M.A. Bocan, et al., *Biochimica et Biophysica Acta*, Vol. 1123, 1992, pp. 133 to 144

Evidence B No. 14, Eve E. Slater, et al., *Drugs* Vol. 36 (suppl. 3), 1988, pp. 72 to 82

Evidence B No. 15, Alfred W. Alberts, *The American Journal of Cardiology*, Vol. 62, 1988, pp. 10J to 15J

Evidence B No. 16, Paper describing CLogP values of CI-981CLogP, July 8, 2015, written by MORIOKA, Hironori

Evidence B No. 17, D. R. Sliskovic, et al., *Journal of Medicinal Chemistry*, Vol. 33, No. 1, 1990, pp. 31 to 38

Evidence B No. 18, a written statement, July 10, 2014, written by KITANO, Yuji, (C 6 in the earlier invalidation trial)

Evidence B No. 19, John I. Germershausen JI, Biochem. Biophys. Res. Commun., Vol. 158, No. 3, 1989, pp. 667 to 675

Evidence B No. 20, Iyakuhin-no Kaihatsu, Vol. 9, Iyakuhin-no Tansaku [II], edited by SAITO, Hiroshi, et al., the front cover, p. 107, and the copyright

page, September 26, 1990, HIROKAWA-SHOTEN LTD.

Evidence B No. 21, An in-house document titled "IW SDZ 264-745 VS. IW SDZ 265-129 PHARMACOLOGY" of AKTIENGESELLSCHAFT, IPA

Evidence B No. 22, A document entitled "Aw's (DC) and IW's (IC)"

Evidence B No. 23, An attested record by Dr. Kathawara in a rosuvastatin calcium patent suit (MDL No. 08-1949), United States District Court for the District of Delaware, July 15, 2009 the front cover, pp. 194 to 197, and pp. 298 to 301

Evidence B No. 24, F. Kathawara, et al., Zenrinsyou Kenkyu Teiansyo, June 1, 1989 p. 1

Evidence B No. 25, United States District Court for the District of New Jersey, Case 1:08-md-01949-JJUF Document 86-2, March 6, 2009 (a writ of summons from United States District Court for the District of New Jersey to Dr. Kathawar)

Evidence B No. 26, an attested record by Dr. Roush in a rosuvastatin calcium patent suit (MDL No. 08-1949), United States District Court for the District of Delaware, March 3, 2010, pp. 1795 to 1798

Evidence B No. 27, a test report, January 22, 2015, written by UENO, Motonobu of SHIONOGI & CO., LTD., (Evidence B No. 49 in the earlier invalidation trial)

Evidence B No. 28, Japanese unexamined patent application publication No. S64-29362

Evidence B No. 29, a specification of U.S. Patent No. 4868185

Evidence B No. 30, a screen of ChemBioDraw Ultra 13.0 where a CLogP value of Evidence A No. 1 of the compound of Exampled 11d is computed, June 6, 2014 Written by SUGINO, Kenichi of SHIONOGI & CO., LTD. (Evidence B No. 40 of the earlier invalidation trial)

Evidence B No. 31, a written opinion, January 27, 2015, written by ITO, Nobuyuki, a professor of the Institute for Liberal Arts and Sciences, Kyoto University, (Evidence B No. 48 in the earlier invalidation trial)

Evidence B No. 32, Japanese published examined application publication No. S64-1476

Evidence B No. 33, a document number search result, conducted by SUEYOSHI, Tsuyoshi, by IPDL relating to Japanese published examined application publication No. S64-1476

Evidence B No. 34, Fergus McTaggart, et al., *The American Journal of Cardiology*, Vol.

87, 2001, pp. 28B to 32B

Evidence B No. 35, an interview form of Crestor tablet ○R (Trial decision note: R in a circle, the same applies hereinafter) March, 2013

Evidence B No. 36, TAKESHIRO, Hideaki, *The Journal of Adult Diseases*, Vo. 33, No. 11, pp. 1398 to 1402, November, 2003

Evidence B No. 37, Peter H. Jones, et al., *The American Journal of Cardiology*, Vol. 92, November, 2003, pp. 152 to 160

Evidence B No. 38, All prescribing information of product name "Crestor" (rosuvastatin calcium) table, 2010, ASTRAZENECA UK LIMITED

Evidence B No. 39, Stephen J. Nicholls, et al., *The American Journal of Cardiology*, Vol. 105, 2010, pp. 69 to 76

Evidence B No. 40, Steven E. Nissen, et al., JAMA, Vol. 295, No. 13, 2006, pp. 1556 to 1565

Evidence B No. 41, TAKAYAMA, Tadateru, et al., *Circulation Journal*, Vol. 73, 2009, pp. 2110 to 2117

Evidence B No. 42, information materials about Crestor tablet 2.5 mg, Crestor tablet 5 mg, Crestor tablet 10 mg, the front cover, the table of contents, pp. 305, ASTRAZENECA UK LIMITED

Evidence B No. 43, a written statement about a reliability criterion of an application material, August 30, 2004, written by a non-clinical general manager (name unknown) of ASTRAZENECA UK LIMITED, (Evidence B No. 51 in the earlier invalidation trial)

Evidence B No. 44, a manager of Evaluation and Licensing Division of Ministry of Health and Welfare Pharmaceutical and Medical Safety Bureau, *Non-clinical pharmacokinetic study guidelines* (PMSB/ELD Notification No. 496), June 26, 1998

Evidence B No. 45, a test report (CYP inhibition assay), January 22, 2015, written by SAKAMOTO, Shingo of SHIONOGI & CO., LTD., (Evidence B No. 53 of the earlier invalidation trial)

Evidence B No. 46, a test report, written by SAKAMOTO, Shingo of SHIONOGI & CO., LTD., (Metabolic stability test), January 22, 2015 (Evidence B No. 54 in the earlier invalidation trial)

Evidence B No. 47, Frank J. Gonzalez, *Pharmacological Reviews*, Vol. 40, No. 4, 1989, pp. 243 to 288

Evidence B No. 48, Saleem Ahmad, et al., *Journal of Medicinal Chemistry*, Vol. 51, No. 9, 2008, pp. 2722 to 2733

Evidence B No. 49, David J Newman, et al., *Future Med. Chem*., Vol, No. 8, 2009, pp. 1415 to 1427

Evidence B No. 50, an Internet article by Bristol-Myers Squibb describing a development article (pipeline) as of February 1, 2014, http://www.bms.com/research/pipeline/ Pages/default.aspx

Evidence B No. 51, *ACCESS TO IYAKUHIN ICHIBA 2013*, TESTA MARKETING INC., March 27, 2013, the front cover, the "investigation summary" page, pp. 22 and 128, and the copyright page

Evidence B No. 52, an article of MIXONLINE entitled "Blockbuster anticancer agents rated as being in the top 15 in the world 2012, Most by disorder, according to MIX", https://www.mixonline.jp/Article/tabid/55/artid/44547/Default.aspx

Evidence B No. 53, an information material entitled "Blockbusters in the world 2012, (summarized by MIX's editorial department)"

Evidence B No. 54, *C&EN*, Vol. 91, No. 49, 2013, the front cover, the table of contents, and p. 14

Evidence B No. 55, an article of MEDSCAPE entitled "Top 100 Most Prescribed, Top Selling Drugs", May 13, 2014, http://www.medscape.com/viewarticle/825023_print

(2) The evidences submitted in the written statement dated March 24, 2016

Evidence B No. 56, *HANREI TIMES*, No. 360, HANREI TIMES Co., Ltd., June 15, 1978, the front cover, p. 148, and the back cover

Evidence B No. 57, a written statement, February 29, 2016, written by MORIOKA, Hironori,

Evidence B No. 58, a written statement, February 25, 2016, written by SUGITA, Kenichi,

Evidence B No. 59, a written statement, February 29, 2016, written by SUEYOSHI, Tsuyoshi,

Evidence B No. 60, an assessment report, Pharmaceuticals and Medical Devices Agency, pp. 1 and 2, September 30, 2004

Evidence B No. 61, a website providing information on rosuvastatin calcium, Pharmaceuticals and Medical Devices Agency, http://www.pmda.go.jp/PmdaSearch/iyakuDetail/GeneralList/2189017F1, March 18, 2016

(3) The evidences submitted in the oral proceedings statement brief
Evidence B No. 62 (the determination 2015 (Gyo-Ke) 10105)

No. 6 Outline of the allegation of the supporting intervener, and the evidences submitted by the intervener
1. Outline of the Allegation Described in a Written Statement and an Oral Proceedings Statement Brief

The outline of the allegation of the supporting intervener is acknowledged as follows; "the body is requested to approve the correction as requested, and approve that the demand for trial of the case was groundless, and the costs in connection with the trial shall be borne by the demandant" (see the written statement dated October 29, 2015, p. 2, "6 the gist of the written statement", and the 1st oral proceedings record, "intervener 2").

The supporting intervener admits that the demandant alleges that neither of the above-described reasons 1 and 2 for invalidation alleged by the demandant has reasons in the written statement dated October 29, 2015 (hereinafter referred to as the "1st written statement by the supporting intervener"), the written statement dated March 24, 2016 (hereinafter referred to as the "2nd written statement by the supporting intervene"), the oral proceedings statement brief, and the written statement dated April 15, 2016 (hereinafter referred to as the "3rd written statement by the supporting intervener").

2. The Evidences Submitted by the Supporting Intervener

The evidences submitted by the supporting intervener is as follows.
(1) The Evidences Submitted in the 1st written statement by the supporting intervener
C 1, all prescribing information of product name "Crestor" (rosuvastatin calcium) tablet, , pp. 1 to 4, August, 2013
C 2, *NANZANDO'S MEDICAL DICTIONARY 18TH EDITION*, NANZANDO Co., Ltd., January 16, 1998, the front cover, p. 932, pp. 1493 and 1494, and the copyright page
C 3, GOSHIMA, Yuichirou, et al., *IGAKU NO AYUMI*, Vo. 153, No. 12, pp. 713 to 740, June 23, 1990
C 4, a brochure entitled "CORTELLISTM FOR COMPETITIVE INTELLIGENCE", THOMSON REUTERS
C 5, an input screen for search conditions of database "CORTELLISTM"
C 6, search Results of database "CORTELLISTM"
C 7, a brochure entitled "THOMSON REUTERS CORTELLISTM COMPETITIVE INTELLIGENCE QUICK GUIDE SERIES: No. 6", THOMSON REUTERS

(2) The Evidences Submitted in the 2nd written statement by the supporting intervener
C 8, a written statement, February 12, 2016, written by MORIOKA, Hironori,
C 9, The Ministry of Health, Labor and Welfare, Iyakuhin SangyoVision 2013, Vol. Information Material, the front cover, the table of contents, and pp. 16, 20, and 36
C 10, John Pears, An information material entitled "CRESTOR: The Benefit-Risk Profile of the Best Statin", pp. PTX1594-0001, 0002, 0006-0009, 0013-0015, 0055, and 0061
C 11, a website of the Ministry of Health, Labor and Welfare, about "Iyakuhin SangyoVision 2013", "Iryokiki Sangyo Vision 2013", June 26, 2013
http://www.mhlw.go.jp/seisakunitsuite/bunya/
kenkou iryou/iryou/shinkou/vision._2013.html

(3) The Evidences Submitted in the oral proceedings statement brief
C 12, a written opinion (Japanese Patent No. 2648897), March 25, 2016, written by IIMURA, Toshiaki,

(4) The Evidences Submitted in the 3rd written statement by the supporting intervener
C 13, Frank D. King, Medicinal Chemistry; Principles and Practice, 1994, Preface, pp. vii to ix

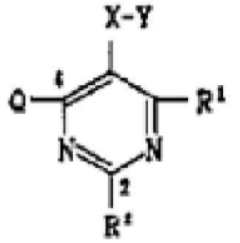
No. 7 Judgment by the Body on the Reasons for Invalidation

The body judges that the patents according to the Inventions 1, 2, 5, and 9 to 12 cannot be invalidated on the basis of the above-described reasons for invalidation and evidences.

The reasons are as follows:

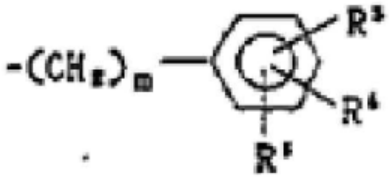
1. Reason 1 for Invalidation
(1) Described Matters in the Evidence A
A Described Matters in Evidence A No. 1

Evidence A No. 1 distributed before the priority date for the Invention discloses the following matters:
(1a) "1. A compound of formula I



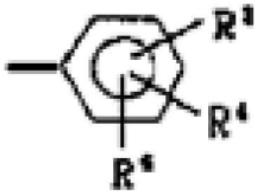
I

wherein
either
R^1 and R^2 independently are:
C_{1-6}alkyl not containing an asymmetric carbon atom;
C_{3-6}cycloalkyl; or

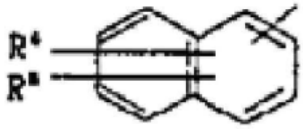


m is 0, 1, 2, or 3;
R^3 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl,
C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;
R^4 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy; and
R^5 is hydrogen, C_{1-2}alkyl, 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 a 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 as defined below;

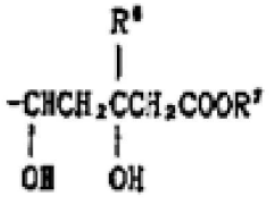
Q is Q' or Q" wherein
Q' is a heterocyclic group optionally mono- or independently
disubstituted by C_{1-2}alkyl or C_{1-2}alkoxy and Q" is either Q"a wherein Q"a is



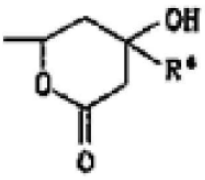
wherein R^3, R^4 and R^3 are as defined
above, including the provisos
thereto,
or Q"b wherein Q"b is



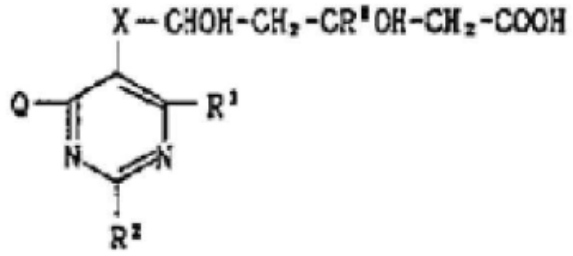
wherein R^4 and R^5 are as defined above;
X is either ethylene or vinylene; and Y is : - a group Y' of formula



wherein
R^6 is hydrogen or C_{1-3}alkyl; and
R^7 is hydrogen, an ester group ($R^{7'}$), or a cation (M);
a group Y" of formula wherein R^6 is as
defined
above; or



- a group Y'" of formula wherein



Ia¹

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 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 in the scope of claims)

(1b) "In particular the compounds show activity in the following tests:

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

The following results are obtained by test A:

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

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

Product of 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 30-hydroxysterol synthesis. The studies are run to test doses between 0.01 mg/kg and 10 mg/kg.

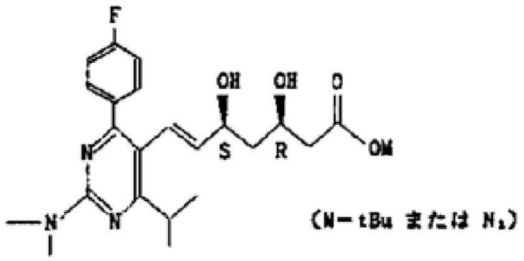
The above test data indicate that the compounds are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis, and, therefore, they are inhibitors of cholesterol

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." (p. 11, the bottom-right column, l. 9 to p. 12, the upper-left column, l. 13).

(1c) "Example 1: (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methyl-ethyl)-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 = a group' Y' wherein R4 = H, R7 = tert-butyl or Na and the configuration is 3R,5S)

[(process variant c) (deprotection) and recovery in salt form]



N-tBu または N2 N-tBu or N_2

a) Deprotection:

14.2 g of (3R,5S)-[E]-3,5-bis[[(1,1-dimethylethyl)-diphenyl-silyl]oxy]-7-[4-(4-fluorophenyl)-6-(l-methylethyl)-2-(dimethyla-mino)pyrimidin-5-yl]-6-heptenoic acid, 1,1-dimethylethyl ester (see below) dissolved in 350 ml CH_3CN is added to a mixture of 47.2 g of tetra n-butylammonium fluoride trihydrate and 350 ml acetonitrile and 9 g (8.6 ml) of glacial acetic acid. This is stirred at 45-50°, and then stirred at 65° for 24 hours under argon. The reaction mixture is poured into 150 ml of saturated sodium chloride solution, 200 ml saturated sodium carbonate solution, and 1.35 liters of water (the pH should be approximately 7.5-8.5 after the addition) and the mixture is extracted three times with diethyl ether. The diethyl ether extracts are 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 is flash chromatographed on a 230-400 ASTM silica gel using 6:4 mixed hexanes: ethyl acetate as the eluant. A yellow oil is isolated which is triturated to a light yellow powder with hexanes. (3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-(di-methylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid,(1,1-dimethylethyl) ester is obtained (M.P. 114-116°;

[α]D^{25} = +7.7°, $CHCl_3$).

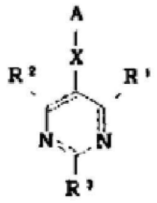
b) Hydrolysis:

12.35 g of the product of step a) above, 26.0 ml of IN NaOH and 150 ml of ethanol are combined and stirred at room temperature for 3-4 hours. The solvent is rotary evaporated. The residue is treated with approximately 150 ml toluene and the toluene is rotary evaporated. This is repeated, and the final residue is triturated to a light yellow solid with a mixture of hexane-ether. This is filtered and dried to yield sodium (3R,5S)-[E]-7-[4-(4-fluoro-phenyl)-6-(1-methylethyl)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoate (M.P. 231-233°; [α]D^{25}= +33.3°, c = 20.625 mg in 1 ml H_2O)." (p. 12, the bottom-left column, l. 3 to p. 13, the upper-left column, l. 3).

B Described Matters in Evidence A No. 2

Evidence A No. 2 distributed before the priority date for the Invention discloses the following matters:

(2a) "1. Substituted pyrimidines of the general formula



(I)

in which

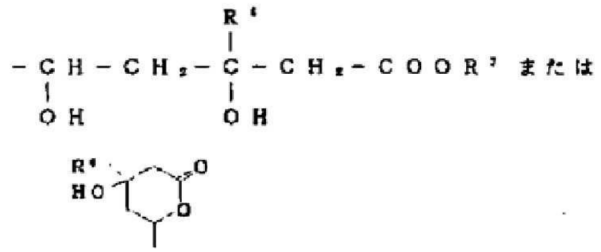
R^1- stands for cycloalkyl or stands for alkyl which can be substituted by halogen, cyano, alkoxy, alkylthio, alkylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl, alkoxycarbonyl, or acyl, or by a group of the formula -NR^4 R^5 wherein

R^4 and R^5 - are identical or different and denote alkyl, aryl, aralkyl, acryl, alkylsulfonyl, or arylsulfonyl, or by carbamoyl, dialkylcarbamoyl, sulphamoyl, dialkylsulphamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsuphonyl, aralkoxy, aralkylthio, or aralkylsulfonyl, where the heteroaryl and aryl radicals of the last-mentioned substituents can be monosubstituted, disubstituted, or trisubstituted by identical or different halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio, or alkylsulfonyl,

R^2 -stands for heteroaryl which can be monosubstituted, disubstituted, or trisubstituted by identical or different halogen, alkyl, alkoxy, alkylthio alkylsulfonyl, aryl, aryloxy, arylthio, arylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio,

or alkoxycarbonyl, or by a group of the formula - NR^4 R^5,
wherein
R^4 and R^5 have the above-mentioned meanings,
or
R^2 - stands for aryl which can be monosubstituted to pentasubstituted by identical or different alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, aryisulfonyl, aralkyl, aralkoxy, aralkylthio, aralkylsulfonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl sulphamoyl, dialkylsulphamoyl, carbamoyl, or dialkylcarbamoyl, or by a group of the formula - NR^4 R^5,
wherein
R^4 and R^5 have the above-mentioned meanings,
R^3- stands for hydrogen or
for cycloalkyl, or
stands for alkyl which can be substituted by halogen, cyano, alkoxy, alkylthio, alkylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl, alkoxycarbonyl, or acyl, or by a group of the formula - NR^4R^5,
wherein
R^4 and R^5 have the above-mentioned meanings,
or by carbamoyl, dialkylcarbamoyl, sulphamoyl, dialkylsulphamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulfonyl, aralkoxy, aralkylthio, or aralkylsulfonyl, where the heteroaryl and aryl radicals of the last-mentioned substituents can be monosubstituted, dlisubstituted, or trisubstituted by identical or different halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio, or alkylsulfonyl, or
R^3- stands for heteroaryl which can be monosubstituted, disubstituted, or trisubstituted by identical or different halogen, alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsulfonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or alkoxy, or by a group of the formula - NR^4R^5,
wherein
R^4 and R^5 have the above-mentioned meanings,
or
R^3- stands for aryl which can be monosubstituted to pentasubstituted by identical or different alkyl, alkoxy, alkylthio, alkylsulfonyl, aryl, aryloxy, arylthio, arylsulfonyl, aralkyl, aralkoxy, aralkylthio, aralkylsulfonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulphamoyl, dialkylsulphamoyl, carbamoyl, or dialkylcarbamoyl, or by a group of the formula - NR^4R^5,
wherein

R^4 and R^5 have the above-mentioned meanings,
or
R^3- stands for alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, or aralkylthio, or for a group of the formula - NR^4R^5,
wherein
R^4 and R^5 have the above-mentioned meanings,
X - stands for a group of the formula -CH_2 -CH_2-
or -CH=CH-,
and
A stands for a group of the formula



または or

wherein
R^6 -denotes hydrogen or an alkyl
and
R^7 - denotes hydrogen,
a methyl, aralkyl, or aryl radical
or
- a cation." (claim 1 in the scope of claims)
(2b) "Surprisingly, the substituted pyrimidines according to the invention show a good inhibitory action on HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase)". (p. 6, the left-bottom column, ll. 2 to 5)

(2c) "If R^7 stands for a cation, then a physiologically tolerable metal cation or ammonium cation is preferably meant. In this connection, alkali metal cations or alkaline earth metal cations such as, for example, sodium cations, potassium cations, magnesium cations, or calcium cations are preferred, and also aluminium cations or ammonium cations, and also non-toxic substituted ammonium cations from amines such as dilower alkylamines (C_9 to about C_6), tritower alkylamines (C_1 to about C_6),

dibenzylamirne, N,N'-dibenzylethyenediamine, N-benzyl-beta-phenylethylamine, N-methytlmorpholine or N-ethylmorpholine, dihydroabiethylamine, N,N'-bis-dihydroabiethylethylenediamine, N-lower alkylpiperidine and other amines which can be used for the formation of salts." (p. 8, the upper-right column, l. 11 to the left-bottom column, l. 7)

(2d) "Particularly preferred compounds of the general formula (I) are those in which

R^1 - stands for cyclopropyl, cyclopentyl, or cyclohexyl, or

stands for methyl, ethyl, propyl, isopropyl, butyl, sec.butyl, or tert.butyl, each of which can be substituted by 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 - stands for pyridyl, pyrimidyl, quinolyl, or isoquinolyl, each of which can be substituted by fluorine, chlorine, methyl, methoxy, or trifluoromethyl, or

- stands for phenyl which can be monosubstituted, disubstituted, or trisubstituted by identical or different methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, methylsulfonyl, ethyl sulfonyl, propyl sulfonyl, isopropylsulfonyl, phenyl, phenoxy, benzyl, benzyloxy, fluorine, chlorine, bromine, cyano, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert-butoxycarbonyl,

R^3 - stands for hydrogen, cyclopropyl, cyclopentyl, or cyclohexyl, or

- stands for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, or isohexyt, each of which can be substituted by fluorine, chlorine, bromine, cyano, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butytsulfonyl, isobutylsulfonyl, tert-butytsulfonyl, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzoyl, acetyl, or ethylcarbonyl, or by a group of the formula $-NR^4R^5$,

wherein

R^4 and R^5 are identical or different and denote methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, phenyl, benzyl, acetyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, or phenylsulfonyl, or by pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, furyl, phenyl, phenoxy, phenylthio, phenylsulfonyl, benzyloxy, benzylthio, or benzylsulfonyl, where the heteroaryl and aryl radicals mentioned above can be substituted by fluorine, chlorine, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, trifluoromethyl, or trifluoromethoxy, or

- stands for thienyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazolyl, isooxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, quinolyl, isoquinolyl, benzoxazolyl, benzimidazolyl, or benzthiazolyl, where the radicals mentioned above can be substituted by 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

- stands for phenyl which can be monosubstituted, disubstituted, or trisubstituted by identical or different 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, bromine, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, or tert.butoxycarbonyl, or by a group - NR^4R^5,

wherein

R^4 and R^5 have the above-mentioned meanings,

R^3 - stands for alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, aralkylthio, or for a group of the formula NR^4R^5,

wherein

R^4 and R^5 have the above-mentioned meanings," (p. 10, the upper-left column, l. 9 from the bottom to p. 11, the left-bottom column, l. 12)

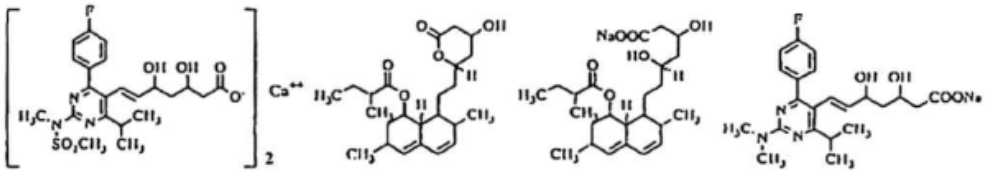
(2e) "Example 8
Methyl erythro-(E)-3,5-dihydroxy-7-[2,6-dimethyl-4-(4-fluorophenyl)-pyrimid-5-yl]-hept-6-enoate" (p. 22, the bottom-left column, ll. 12 to 15)
(2f) "Example 15 Methyl erythro-(E)-3,5-dihydroxy-7-[4-(4-fuorophenyl)-6-methyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate" (p. 24, the upper-right column, ll. 1 to 5)
(2g) "Example 23
Methyl
erythro-(E)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-6-isopropyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate" (p. 26, the upper-left column, l. 5 from the bottom to the last line)

C Described Matters in Evidence A No. 3
Evidence A No. 3, which is an internal document by the patentee of the present case entitled "Managerial challenge report", describes the following matters:
(3a) "[Prolusion]

An HMG-CoA reductase inhibitors S-4522 has been developed as a cholesterol reducer, and a phase II trial thereof has been carried out presently. Meanwhile, preparation to file an EU patent application of the inhibitor is in process, and comparison data of SDZ-65129 (SANDOZ) that is a compound of the preceding patent and HMG-CoA reductase-inhibiting activity are required in the patent examination. We already have reported that S-4522 indicates inhibiting activity nine times stronger than that of SDZ-65129 [1)]; however, SDZ-65129 described in the publication of unexamined patent application of SANDOZ has inhibiting activity about 13.5 times stronger than that of mevinolin (or Lovastatin, MSD) that is a contrast medicine [2)], and shows that S4522 is about two times stronger than that of the same Mevinonin (Trial decision note: Mevinonin is found to be an error of Mevinolin) [3)], and the SDZ-65129 has inhibiting activity reversely stronger than that of S4522 as long as they are compared based on the data described in the patent. The contradictory result is considered to be obtained because the inhibiting activity (IC_{50} value) of the Mevinolin that we used as a contrast medicine is markedly different from that used by SANDOZ. That is, while the IC_{50} value of mevinolin of SANDOZ is 352 nM, our data show the IC value of 23 nM, which is different by a factor of more than ten times. There is no essential difference between the experimental methods, so that the chemical states of the used mevinolins are highly likely to be different from each other between ours and SANDOZ's. While normally having a lactone ring in its part of the constitution, mevinolin has no effect as it is, but when the lactone cleaves in vivo to be a carboxylic acid, mevinolin exerts its effect. We observe HMG-CoA reductase-inhibiting activity

in the latter sodium carboxylate; however, SANDOZ is highly likely to see it in the former sodium carboxylate.

In order to reveal this, we compared four compounds of S4522, the sodium carboxylate of mevinolin (mevinolin Na), a lactone body, and SDZ-65129 in terms of inhibiting activity in a parallel test.



S-4522　　メビノリン(ラクトン)　　メビノリン Na　　SDZ-65129

メビノリン（ラクトン）　　Mevinolin (lactone)
メビノリンＮａ　　Mevinolin Na

"(P. 1, ll. 1 to 21, and Chemical formula)
(3b) "[Result and Discussion]

S-4522, SDZ-65129, mevinolin Na, and HMG-CoA reductase-inhibiting activity in rat-liver microsome of a lactone body is indicated in the following table.

ラット肝ミクロソーム HMG-CoA 還元酵素に対する阻害活性

阻害剤	IC_{50}, nM
メビノリン Na	28 ± 9
メビノリン(ラクトン)	1830 ± 360
S-4522	14 ± 3
SDZ-65129	31 ± 11

値は 3 回の実験の平均 ± 標準誤差

ラットHMG－CoA　還元酵素に対する阻害活性
HMG-Coa Reductase-Inhibiting Activity in Rat-Liver Microsome

阻害剤　　Inhibitor
メビノリンＮａ　　Mevinolin Na
メビノリン（ラクトン）　　Mevinolin (lactone)
値は３回の実験の平均±標準誤差　　The values indicate average±standard errors in three experiments.

IC_{50} value of mevinolin Na of two kinds of mevinolins used as a contrast medicine is 28±9 nM, which is very close to the value of the conventionally result (IC_{50}=23 nM)[3]. Meanwhile the lactone body has activity of 1830±360 nM, which is 1/60 to 1/70 that of the mevinolin Na, which shows markedly reduced inhibiting activity by lactonization. Based on this result, we made a guess about whether the mevinolin (IC_{50}=352 nM) of SANDOZ is a carboxylic acid or a lactone body, and considered that the mevinolin of SANDOZ is highly likely to be a lactone body as having activity closer to that of the lactone body, because the mevinolin of SANDOZ has inhibiting activity of about 1/13 that of mevinolin Na and about five times larger than that of the lactone body. At this time, S-4522 had inhibiting activity of 14±3nM which is two times larger than that of mevinolin Na, and SDZ-65129 had inhibiting activity almost equal to 31±11 nM. We previously reported that S-4522 indicates inhibiting activity nine times stronger than that of SDZ-65129; however, the difference between them shown in this experiment is about two times. The difference is interpreted to be within a range of variability in view of experimental accuracy and the like because the IC_{50} values of S-4522 and SD-65129 are about twofold larger or smaller variations of those obtained previously (7.2 nM and 65 nM, respectively) (1).

The above-described result shows that the mevinolin used in comparing SDZ-65129 by SANDOZ is highly likely to be a lactone body (in an inactive form), and thus shows that the HMG-CoA reductase-inhibiting activity of S-4522 must be stronger than that of SDZ-65129. The lactone body of mevinolin has no meaning other than a prodrug, so that a result in a carboxylic acid in an active form is considered important for evaluation of enzyme-inhibiting activity in vitro." (p. 2, l. 11 to p. 3, l. 5)

D Described Matters in Evidence A No.5

Evidence A No. 5, which is an internal document of the patentee of the present case entitled "Past Q & A with ZENECA about S-4522 patent", describes the following matters in its Japanese translated sentences:

(5a) "○2 (Trial decision note: 2 in a circle) Second response (about variation in comparative data with SANDOZ, December 24, 1997)

(1) As a result of discussion with our researcher (Mr. Goro Kato), we (trial decision note: SHIONOGI & CO., LTD.) confirmed that data possible to be provided on comparison between S-4522 and SDZ-65129 by SANDOZ (Example 1 in the description of EP publication No. 367895 (translator's notes: a corresponding EP

application of Evidence A No. 1)) only provides four measurement data indicated below.

［HMG－ＣｏＡ還元酵素に対するＩＣ５０（ｎM）］

測定	Ｓ－４５２２	サンドー６５１２９	日
1	２０	５２	１９９６年７月２４日～１９９６年８月１日
2	９．６	１４	
3	１３	２７	
測定１～３の平均	１４	３１	
4	７．２	６５．５	１９９３年１２月７日

［HMG－Ｃｏａ還元酵素に対するＩＣ５０（ｎｍ)］

[IC50 (nM) to HMG-CoA reductase]

測定　Measurement

測定１～３の平均　Average among 1st measurement to 3rd measurement

サンドー６５１２９　SANDOZ-65129

日　Date

１９９６年７月２４日～１９９６年８月１日　July 24, 1996 to August 1, 1996

１９９３年１２月７日　December 7, 1993

Each measurement was overseen by Mr. Kato, and the 4th measurement was carried out on a different day from the 1st measurement to the 3rd measurement. Thus, as seen in the table, there is digital inconsistency among the values. We apologize to you (trial decision note: ZENECA) for any confusion.

Mr. Kato has no idea about why the measurement values varied, but he considers that the variations are within the allowable range, and can be explained partially as variations that were caused by the assay technology, pipetting, and measurement carried out in the experiments, and a variety of other operations. In addition, the difference between the used samples and test reagents (isotope and the like), the lot difference between the used materials, the problem in stability of enzyme source activity, and the differences between experimenters or experimental laboratories are considered to be elements contributing to the variations". (p. 5, ll. 1 to 17).

E Described Matters in Evidence A No. 7

Evidence A No. 7, which had been distributed before the priority date for the Invention, describes the following matters in its Japanese translated sentences:

(7a) "Relationship between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase" (p. 463, the left column, pp. 37 to 39)

(7b) "It is now well-established that inhibition of the enzyme HMG-CoA reductase (HMGR) is an effective means for lowering plasma total and LDL-cholesterol in hypercholesterolemic patients [1]. However, the long-term safety of these agents is still unproven. ... Recently, there has been considerable controversy in the literature regarding both the nature and existence of tissue (liver) selectivity for various HMGR inhibitors, and whether confining their action to the liver could reduce the incidence of adverse reactions. ... It has been proposed that tissue selectivity is influenced primarily by the relative lipophilicity of the drugs, with relatively more hydrophilic compounds showing higher liver selectivity [10].

Since we had prepared HMGR inhibitors possessing considerable variation in constitution and lipophilicity during the course of our program in this area, we decided to test this hypothesis directly. Thus, we compared a selection of potent inhibitors possessing a broad range of calculated lipophilicities (CLOGP) for their abilities to inhibit sterol synthesis in tissue cubes derived from rat liver, spleen, and testes. The results of these studies are the subject of this report.

チャートI

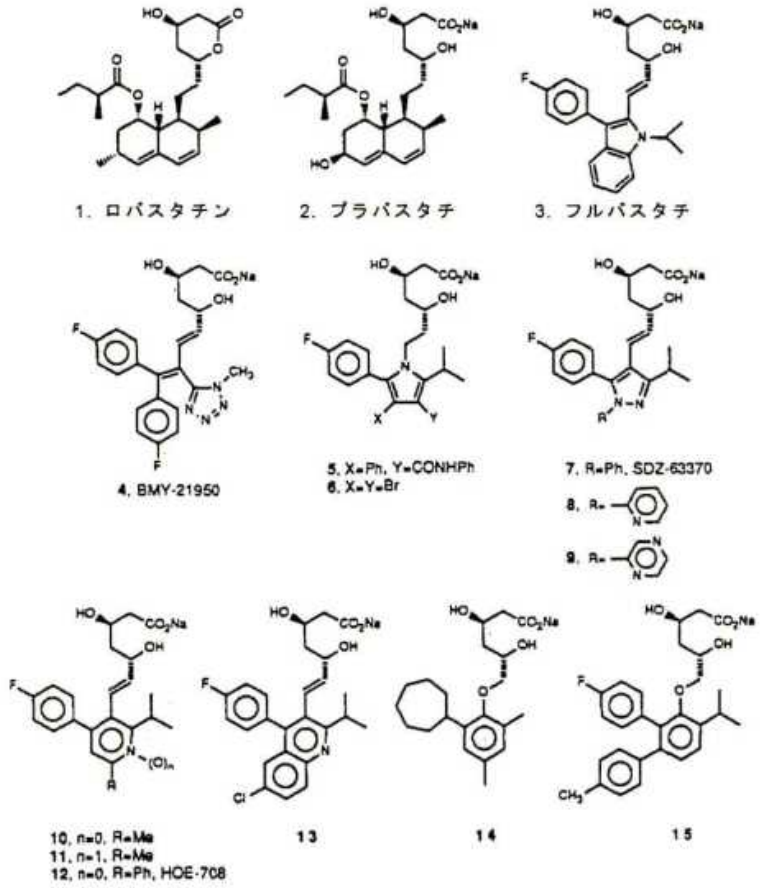


Chart I

1. Lovastatin

2. Bravastati

3. Fluvastati

(Trial decision note: : "2. Bravastati" is an error of " 2. Pravastatin", and "3. Fluvastati" is an error of " 3. Fluvastatin") (p. 463, the left column, l. 40 to the right column, l. 25)

(7c) "

表 I

化合物	CLOGP [a]	IC_{50}, nM				IC_{50} 比	
		HMGR [b]	肝臓 [c]	脾臓 [c]	精巣 [c]	脾臓/肝臓	精巣/肝臓
11 [d]	0.04	9.4	18	266	718	14.8	39.9
2 [e]	0.51	40.0	141	228	329	1.6	2.3
4 [f]	0.52	13.0	108	1579	638	14.6	5.9
9 [g]	0.73	6.6	10	20	64	2.0	6.4
8 [g]	1.86	10.0	17	29	82	1.7	4.8
10 [h]	2.32	7.7	71	9	17	0.13	0.24
1 [i]	3.11	13.0	28	5	4	0.17	0.14
3 [j]	3.24	32.0	142	292	4	2.10	0.03
14 [g]	3.69	141.0	5170	108	63	0.02	0.01
7 [k]	3.70	7.2	34	12	8	0.35	0.24
12 [h]	3.92	2.0	8070	77	16	0.01	0.002
13 [l]	3.94	480.0	6280	92	184	0.02	0.03
6 [l]	4.02	26.0	2726	140	24	0.05	0.009
5 [l]	4.06	7.5	39	29	36	0.74	0.9
15 [g]	4.82	100.0	6037	375	511	0.06	0.08

表 I	Table I
化合物	Compound
肝臓	Liver
脾臓	Spleen
精巣	Testes
ＩＣ５０比	IC_{50} ratio

a Calculated log P (Med Chem Ver 3.54) of a dihydroxy acid.

b HMG-CoA reductase-inhibiting activity in rat-liver microsome fraction. See Reference document 14. ..." (p. 464, Table I)

(7d) "As a biological result, there were many evidences showing that ring-opening dihydroxy acids in lovastatin, pravastatin, and the other HMG-CoA reductase-inhibiting activity were primary active portions that circulate in blood plasma [13], so that all the compounds were examined in this form. Firstly, abilities of the compounds to inhibit microsome HMGR in vitro were examined as evaluations of inherent effects [14]. Then, as evaluation to compare the effects on liver with the effects on periphery, effects of the compounds on the uptake of [^{14}C] acetate salts in sterol were measured in the tissue

cubes derived from rat liver, spleen, and testes [15]. The examination of these research results indicates that there exist significant differences between the compounds, and lipophilicity is an important factor (Table I, the compounds are indicated in increasing order of lipophilicity). Thus, each of the compounds having CLOGP<2 (Compounds 11, 2, 4, 9, and 8) is considered to possess medium degree of tissue selectivity indicated by "tissue/liver ratio>1. In general, the compounds having CLOGP<2 are more effective in peripheral tissues than liver tissues. There are two exceptions; Compound 5 is equally effective in liver tissues and peripheral tissues, and Compound 3 strongly inhibits sterol synthesis in testes while it does not inhibit synthesis in spleen." (p. 464, the left column, l. 17 to the last line in the right column)

(7e) "As indicated above, the "threshold point" at which the selectivity becomes equal in liver tissues and other tissues is CLOGP= (Trial decision note: a symbol with "~"above "=") 2. When the threshold point is below this value, the compounds are very selective with respect to liver tissues, and when the threshold point is above this value, the compounds are very selective with respect to peripheral tissues." (p.465, the left column, ll. 8 to 12)

F Described Matters in Evidence A No. 8

Evidence A No. 8 that had been distributed before the priority date for the Invention describes the following matters in its Japanese translated sentences:

(8a) "HMG-CoA reductase inhibitors: stimulative progress in treatment of hyperlipoproteinemia" (P. 121, Title)

(8b) "Strong inhibitors of a beta-hydroxy-beta-methyl-glutaryl CoA reductase (HMG-CoA reductase, EC1. 1. 1. 34) that controls a major process of endogenous synthesis of cholesterol have recently been drawing increasing attention in order to find an effective and safe curative medicine to lower LDL cholesterol. Studies using HMG-CoA reductase inhibitors such as compactin (mevastatin), CS-514 (pravastatin...), mevinolin (lovastatin...), and synvinolin (simvastatin...) that have very deep relation in constitution with one another have been reported both in animals and humans." (p. 122, ll. 14 to 22)

(8c) "

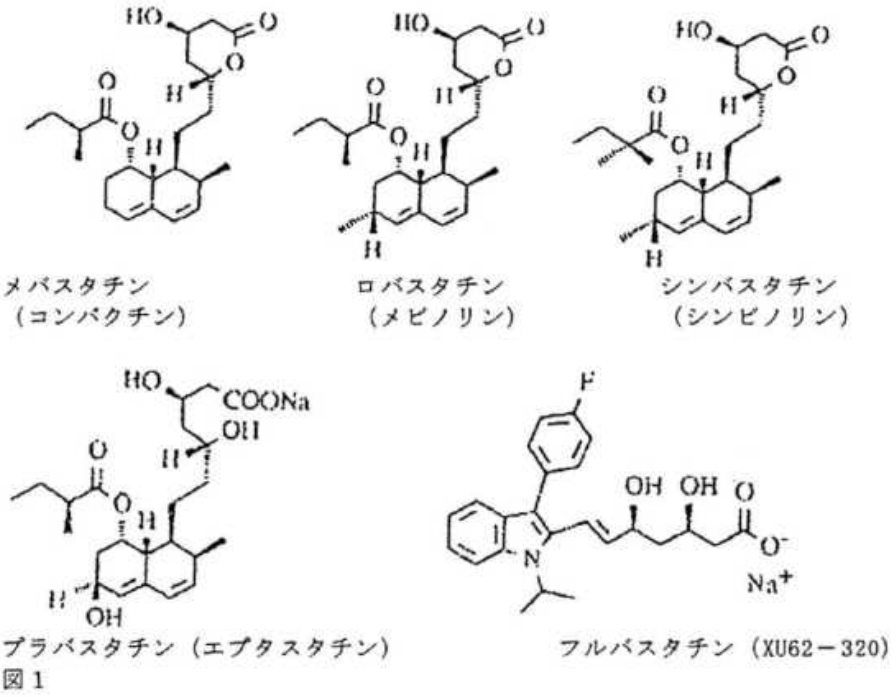


図１

メバスタチン（コンパクチン）	Mevastatin (compactin)
ロバスタチン（メビノリン）	Lovastatin (mevinolin)
シンバスタチン（シンビノリン）	Simvastatin (synvinolin)
プラバスタチン（エプタスタチン）	Pravastatin (eptastatin)
フルバスタチン	fluvastatin
図１	FIG. 1

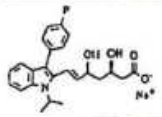
" (p. 123. FIG. 1)

(8d) "Results of in vitro microsomal assay of HMG-CoA reductase and biosynthesis assay of cholesterol

All the initial studies to analyze the inhibitory abilities of a variety of compounds against the HMG-CoA reductase were carried out using the assay of the HMG-CoA reductase activity described in reference document 14 using a rat liver microsomal suspension that had been just prepared from a male Sparague-Dawley rat." (p. 133, ll. 9 to 14)

(8e) "Table 1 Comparison of Microsomal HMG-CoA reductase inhibitory activity

Table 1
Comparison of Microsomal HMG-CoA Reductase Inhibitory Activity

	Compound	IC_{50} (μM)	Relative Potency*
	XU 62-320	0.0069	146.1
	Compactin	1.011	1.0
	Lovastatin	0.352	2.8
	Na Salt Compactin	0.154	6.5
	Na Salt Lovastatin	0.068	14.8

」（第１３４頁Table1）

" (p. 134, Table 1)

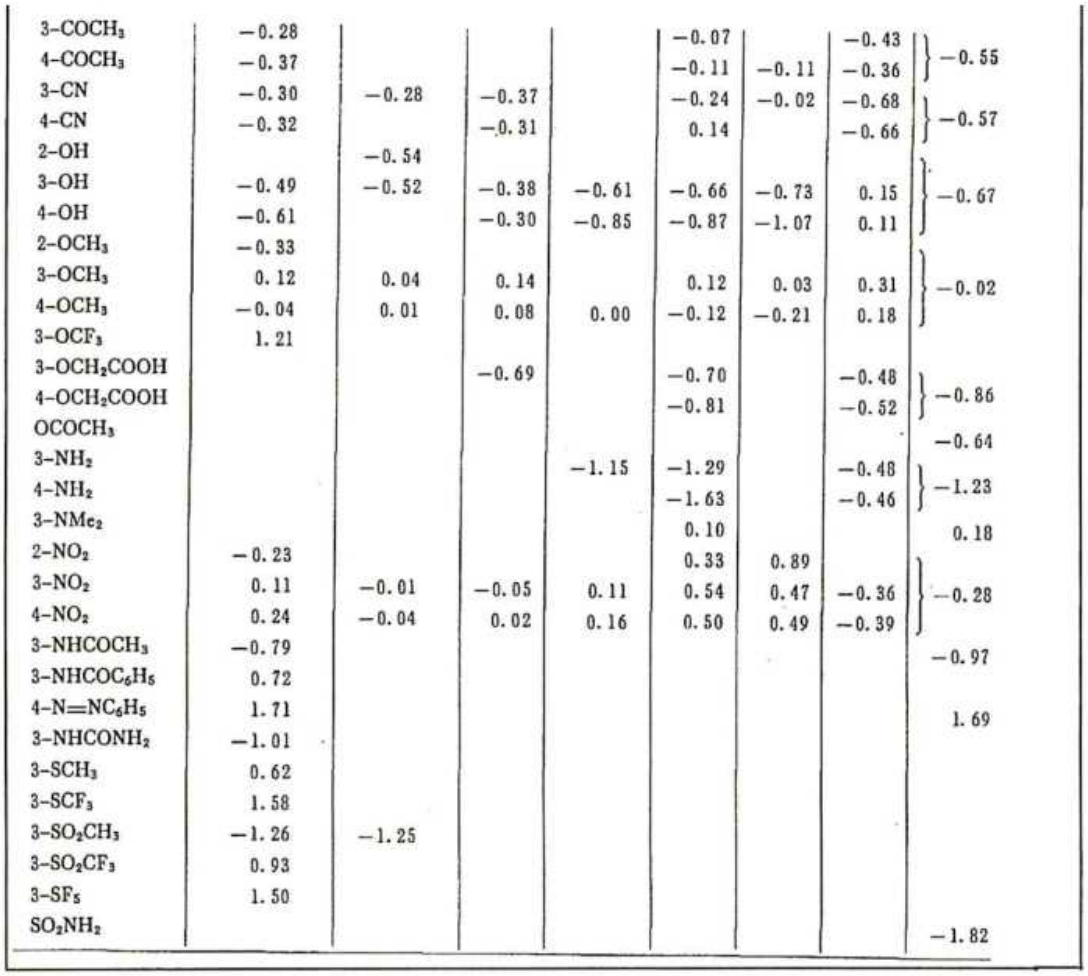
G Described Matters in Evidence A No. 9

Evidence A No. 9, which had been distributed before the priority date for the Invention, describes the following matters.

(9a) "

表 7.5 π_X 值（芳香族置换体  ）(Tute[3])

X	R							
	$-OCH_2CO_2H$	$-CH_2CO_2H$	$-CO_2H$	$-CH_2OH$	$-OH$	$-NH_2$	$-NO_2$	H
H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2-F	0.01	0.04			0.25			
3-F	0.13	0.19	0.28		0.47	0.40		0.14
4-F	0.15	0.14	0.19		0.31	0.25		
2-Cl	0.59				0.69			
3-Cl	0.76	0.68	0.83	0.84	1.04	0.98	1.61	0.71
4-Cl	0.70	0.70	0.87	0.86	0.93	0.80	0.54	
2-Br	0.75				0.89			
3-Br	0.94	0.91	0.99		1.17	1.13	0.79	0.86
4-Br	1.02	0.90	0.98		1.13	1.12		
2-I	0.92				1.19			
3-I	1.15	1.22	1.28		1.47			
4-I	1.26	1.23	1.14		1.45	1.39		
2-Me	0.68							
3-Me	0.51	0.49	0.52	0.50	0.56	0.50	0.57	0.56
4-Me	0.52	0.45	0.42	0.48	0.48	0.49	0.52	
2-Et	1.22							
3-Et	0.97				0.94			
3-*n*-Pr	1.43							
3-*i*-Pr	1.30							
4-*i*-Pr	1.40							
3-*n*-Bu	1.90							
4-*s*-Bu	1.82							
3-*t*-Bu	1.68							
4-Cyclopentyl	2.14							
4-Cyclohexyl	2.51							
$3-C_6H_5$	1.89							
$3,4-(CH_2)_3$	1.04							
$3,4-(CH_2)_4$	1.39							
$3,4-(CH)_4$	1.24							1.24
$3-CF_3$	1.07	1.16	1.07		1.49	1.28		
$3-CH_2OH$					−1.02	−0.95	−0.65	−1.03
$4-CH_2OH$					−1.26		−0.60	
$3-CH_2COOH$					−0.61		−0.40	−0.72
$4-CH_2COOH$							−0.47	
3-COOH	−0.15	−0.32	−0.19		0.04		−0.02	−0.28
4-COOH					0.12		0.03	
$CONH_2$								−1.49
$3-COOCH_3$			−0.05					−0.01
$2-COCH_3$	0.01							



3-$COCH_3$	−0.28				−0.07		−0.43	−0.55
4-$COCH_3$	−0.37				−0.11	−0.11	−0.36	
3-CN	−0.30	−0.28	−0.37		−0.24	−0.02	−0.68	−0.57
4-CN	−0.32		−0.31		0.14		−0.66	
2-OH		−0.54						
3-OH	−0.49	−0.52	−0.38	−0.61	−0.66	−0.73	0.15	−0.67
4-OH	−0.61		−0.30	−0.85	−0.87	−1.07	0.11	
2-OCH_3	−0.33							
3-OCH_3	0.12	0.04	0.14		0.12	0.03	0.31	−0.02
4-OCH_3	−0.04	0.01	0.08	0.00	−0.12	−0.21	0.18	
3-OCF_3	1.21							
3-OCH_2COOH			−0.69		−0.70		−0.48	−0.86
4-OCH_2COOH					−0.81		−0.52	
$OCOCH_3$								−0.64
3-NH_2				−1.15	−1.29		−0.48	−1.23
4-NH_2					−1.63		−0.46	
3-NMe_2					0.10			0.18
2-NO_2	−0.23				0.33	0.89		
3-NO_2	0.11	−0.01	−0.05	0.11	0.54	0.47	−0.36	−0.28
4-NO_2	0.24	−0.04	0.02	0.16	0.50	0.49	−0.39	
3-$NHCOCH_3$	−0.79							−0.97
3-$NHCOC_6H_5$	0.72							
4-$N{=}NC_6H_5$	1.71							1.69
3-$NHCONH_2$	−1.01							
3-SCH_3	0.62							
3-SCF_3	1.58							
3-SO_2CH_3	−1.26	−1.25						
3-SO_2CF_3	0.93							
3-SF_5	1.50							
SO_2NH_2								−1.82

表７．５　πx 値（芳香族置換体）　　Table 7.5 πx Value (Aromatic Substituent)

" (pp. 134 to 135)

(9b) "In "*DRUG DESIGN*", it is very useful and important that log P or π indicates additive properties as described above, which can not only evaluate a bond between one compound and one protein but also evaluate the ability of a compound to reach its reaction point under some conditions, whereby the relative lipophilicity of acting molecules that are to be prepared now can be predicted if merely paper and a pencil are available.　For example, in diphenylhydramine (7.2), 4.26 with respect to two benzene rings, there are used 0.30 with respect to a methyl group that is obtained by subtracting 0.20 of branch from 0.50 of the methyl group, -0.98 of OCH_3 value (if the πx value is used, the value becomes 3.64 to fall within the margin of error of 10%) in πx' in Table 7.4 (supposing that a side chain is bent on a ring in a liquid solution) as -OCH_2-,

-$N(CH_3)_2$ values, and the calculated values match the actual measured values are well matched.

Using a similar calculation in diethylstilbestrol (7.3), log P matches an actual measured value 5.07 and a calculated value 5.22*.

There are a variety of approaches as the above-described calculation approach; however, there is no big difference among the values even using any approaches.

Table 7.5 shows a table by Tute [3)] for reference that shows πx values of aromatic substituents." (p.135, the 4th line from the bottom to p. 136, l. 7)

H Described Matters in Evidence A No. 10

Evidence A No. 10, which had been distributed before the priority date for the Invention, describes the following matters.

(10a) "14.7 Cholesterol Biosynthesis

We normally synthesize about 1.5 to 2.0 g of cholesterol per day, and most of it is synthesized in the liver (1.0 to 1.5 g/day). As described above (in Chapter 3 "Lipid and Biomembrane"), cholesterol is used to constitute biomembranes, and is necessary in order to synthesize bile acid and steroid hormone. Synthesis of cholesterol is very complicated, and 25 specific enzymatic stages relate to the synthesis. Being so complicated, the route is simplified to be drawn (see FIG. 14-1-1)." (p. 254, ll. 1 to 8)

I Described Matters in Evidence A No. 11

Evidence A No. 11, which had been distributed before the priority date for the Invention, describes the following matters.

(11a) "Cholesterol is referred to also as cholesterin. $C_{27}H_{46}O$, Molecular mass: 386.66. The most representative sterol. A cyclopentanone phenanthrene ring has an OH group in C-3, and a side chain in C-17. A needle-like crystal (recrystallize from ethanol), a fusing point; 149 degrees C, a specific optical rotation [α]; D-39 degrees (in chloroform), insoluble in water, alkali, and acid, generally readily-soluble in an organic solvent while hardly-soluble in petroleum ether, cold acetone, and cold alcohol. Cholesrterol forms a hardly-soluble molecular compound with digitonin, is widely distributed throughout the animal world, and is contained in cranial nerve tissues, adrenal glands, and other organs in considerable amounts. Cholesterol forms a constituent element of a cell membrane, an organelle membrane, and a myelin sheath as a steady component for cells, and is an important lipid that becomes a precursor of bile, gonadal hormone, adrenal cortex hormone, vitamin D, and the like. Cholesterol is present in a total amount of about 0.2% of the body's weight normally with cholestenol

or 7-dehydrocholesterol. Cholesterol is of free type, or is partially an ester of aliphatic acid (→ (Trial decision note: different font, the same shall apply hereinafter) cholesterol ester). The principal organ for cholesterol metabolism is the liver. 90% of cholesterol biosynthesis is carried out in the liver and the wall of the small intestine. The synthesis starting from acetyl CoA to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), mevalonic acid*, and squalene*is adjusted by HMG-CoA reductase*. To be specific, synthetic control of HMG-CoA reductase is carried out in accordance with the amount of cholesterol that enters cells via receptors of beta-lipoproteins, and as a result thereof, cholesterol synthesis is adjusted." (p. 489, the right column, l. 43 to p. 490, the left column, l. 11)

(11b) "A hydoroxymethylglutaryl-CoA reductase EC1.1.1.88. is abbreviated as an HMG-CoA reductase. A hydoroxymethylglutaryl-CoA reductase is an enzyme to reduce hydoroxymethylglutaryl-CoA in the presence of NADPH to catalyze the reaction to generate a mevalonic acid*, and this reduction reaction is a two-step reaction in which one of carboxyl groups of ground substances is reduced to a hydroxyl group via an aldehyde group. The enzyme is an important regulatory point for biosynthesis of cholesterol, a variety of steroids, and terpene (→biosynthesis of steroid, biosynthesis of terpene). Thus, the enzyme varies in activity according to a variety of ambient conditions, dietary conditions, and the like.″ (p. 1010, the left column, 9th line from the bottom to the right column, l. 2)

J Described Matters in Evidence A No. 14

Evidence A No. 14, which had been distributed before the priority date for the Invention, describes the following matters in its Japanese translated sentences:

(14a) "

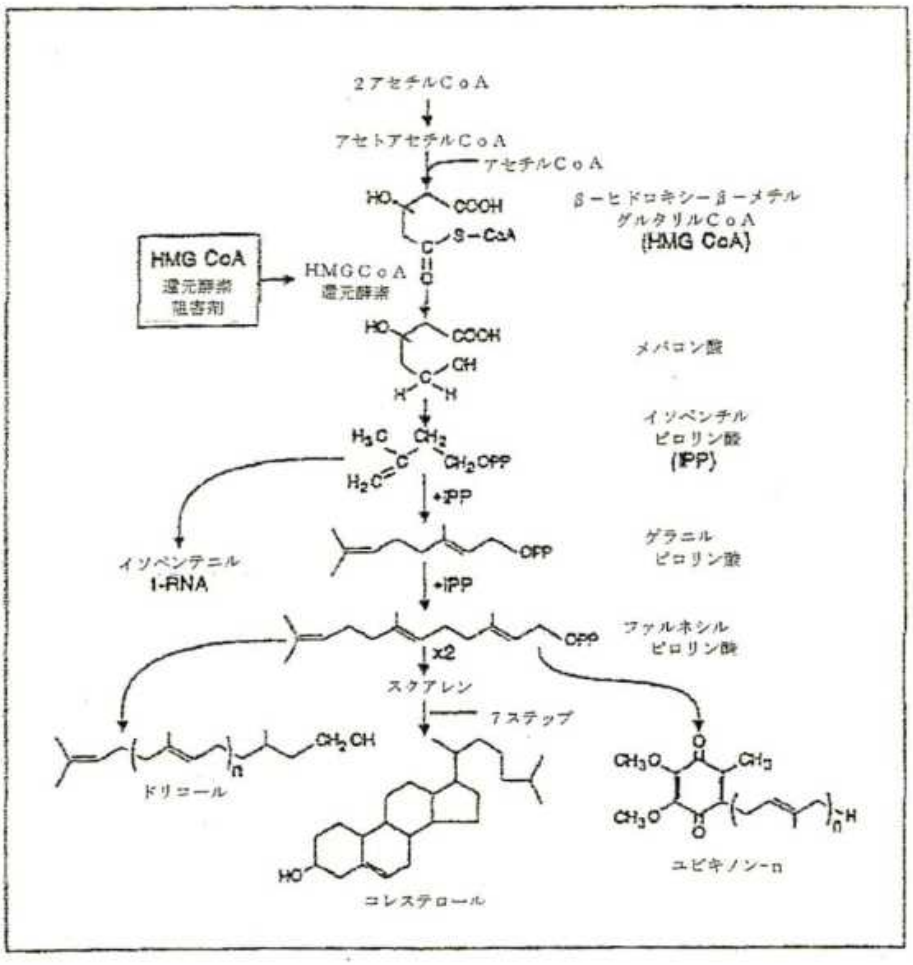


図２　コレステロール及びメバロン酸の他の生成物の合成工程

２アセチルＣｏＡ	2 acetyl CoA
アセトアセチルＣｏＡ	Acetoacetyl CoA
アセチルＣｏＡ	Acetyl CoA
β－ヒドロキシ－β－メチル　グルタリルＣｏＡ	Beta-Hydroxy-Beta-Methyl-Glutaryl CoA
ＨＭＧ　ＣｏＡ　還元酵素阻害剤	HMG-CoA reductase inhibitors
ＨＭＧ　ＣｏＡ　還元酵素	HMG-CoA Reductase
メバロン酸	Mevalonic Acid
イソペンチル　ピロリン酸	Isopentenyl Pyrophosphate
ゲラニル　ピロリン酸	Geranyl Pyrophosphate
ファルネシル　ピロリン酸	Farnesyl Pyrophosphate
ユビキノン－ｎ	Ubiquinone-N
イソペンテニル	Isopentenyl

スクアレン	Squalene
７ステップ	7 Step
ドリコール	Dolichol
コレステロール	Cholesterol

図２　コレステロール及びメバロン酸の他の生成物の合成工程

FIG. 2 Synthesis Process of Cholesterol and Other Products of Mevalonic Acid

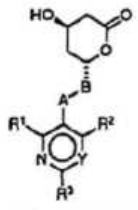
Dolichol contains isoprenyl groups of a variety of numbers ([n] 19 to 24). In the case of Ubiquinone-N, the number (n) of the groups in vertebrate animals is nine to ten. HMG-CoA reductase inhibitors competitively inhibit HMG-CoA, which is a rate-controlling factor of cholesterol synthesis." (p. 25, the right column, Figure 2)

K Described Matters in Evidence A No. 16

Evidence A No. 16, which had been distributed before the priority date for the Invention, describes the following matters in its Japanese translated sentences:

(16a) "Lactones 2 to 4 of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoic acid (heptane) were synthesized. By broadly searching the connection between the constitution and the activity, a few kinds of compounds that surpass the inhibiting activity of Mevinolin (lb) against HMG-CoA were found both in vitro and in vivo. The first clinical trial (HR780) by 2i is in preparation." (p. 52, Abstract)

(16b) "Table I: Physical Characteristics and Inhibiting Activity of Lactones 2 to 4



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

no.	Y	R^1	R^2	R^3	purifien[a]	% yield[b]	formula	mp, °C	anal.[c]	IC_{50},[d] nM
1b	–	–	–	–	–	–	–	–	–	8
2a	CH	CH_3	4-FC_6H_4	CH_3	A	16	$C_{20}H_{20}FNO_3$	205	C, H, F, N	260
2b	CH	CH_3	4-ClC_6H_4	CH_3	A	15	$C_{20}H_{20}ClNO_3$	oil	C, H, Cl, N	94
2c	CH	CH_3	4-FC_6H_4	C_6H_5	B	13	$C_{25}H_{22}FNO_3$	149	C, H, F, N	38
2d	CH	C_2H_5	4-FC_6H_4	C_6H_5	C	13	$C_{26}H_{24}FNO_3$	oil	C, H, F, N	40
2e	CH	*i*-C_3H_7	4-FC_6H_4	CH_3	C	23	$C_{22}H_{24}FNO_3$	oil	C, H, F, N	9
2f	CH	*i*-C_3H_7	4-FC_6H_4	*i*-C_3H_7	C	28	$C_{24}H_{28}FNO_3$	137–140	C, H, F, N	3
2g	CH	*i*-C_3H_7	4-FC_6H_4	*t*-C_4H_9	C	16	$C_{25}H_{30}FNO_3$	158–160[e]	C, H, F, N	1
2h	CH	*i*-C_3H_7	4-FC_6H_4	*c*-C_6H_{11}	C	13	$C_{27}H_{32}FNO_3$	135–138	C, H, F, N	4
2i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	C	24	$C_{27}H_{26}FNO_3$	141[f]	C, H, F, N	3
2j	CH	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{27}H_{25}F_2NO_3$	oil	C, H, F, N	2
2k	CH	*i*-C_3H_7	4-FC_6H_4	2,5-$(CH_3)_2C_6H_3$	C	28	$C_{29}H_{30}FNO_3$	oil	C, H, F, N	5
2l	CH	*i*-C_3H_7	4-FC_6H_4	3,5-$(CH_3)_2C_6H_3$	C	26	$C_{29}H_{30}FNO_3$	80	C, H, F, N	8
2m	CH	*i*-C_3H_7	4-$CH_3OC_6H_4$	C_6H_5	C	30	$C_{28}H_{29}NO_4$	oil	C, H, N	13
2n	CH	*i*-C_3H_7	4-$CF_3C_6H_4$	C_6H_5	C	21	$C_{28}H_{26}F_3NO_3$	oil	C, H, F, N	36
2o	CH	*t*-C_4H_9	4-FC_6H_4	C_6H_5	C	19	$C_{28}H_{28}FNO_3$	oil	C, H, F, N	18
2p	CH	*c*-C_6H_{11}	4-FC_6H_4	C_6H_5	C	11	$C_{33}H_{32}FNO_3$	196–198	C, H, F, N	30
2q	CH	4-FC_6H_4	*i*-C_3H_7	C_6H_5	C	25	$C_{27}H_{26}FNO_3$	oil	C, H, F, N	4
2r	N	CH_3	4-FC_6H_4	CH_3	D	18	$C_{19}H_{19}FN_2O_3$	174–176[h]	C, H, F, N	500
2s	N	CH_3	4-ClC_6H_4	CH_3	D	20	$C_{19}H_{19}ClN_2O_3$	oil	C, H, Cl, N	600
2t	N	*i*-C_3H_7	4-FC_6H_4	*i*-C_3H_7	E	13	$C_{23}H_{27}FN_2O_3$	oil	C, H, F, N	3
2u	N	*i*-C_3H_7	4-FC_6H_4	*c*-C_6H_{11}	C	19	$C_{25}H_{31}FN_2O_3$	128	C, H, F, N	1
2v	N	*i*-C_3H_7	4-FC_6H_4	C_6H_5	D	18	$C_{26}H_{25}FN_2O_3$	164–166[i]	C, H, F, N	3
2w	N	*i*-C_3H_7	4-FC_6H_4	4-FC_6H_4	C	22	$C_{26}H_{24}F_2N_2O_3$	138–140	C, H, F, N	1
3a	CH	CH_3	4-FC_6H_4	CH_3	A	8	$C_{20}H_{20}FNO_3$	188	C, H, F, N	>1000
3c	CH	CH_3	4-FC_6H_4	C_6H_5	B	8	$C_{25}H_{22}FNO_3$	216	C, H, F, N	100
3s	N	CH_3	4-ClC_6H_4	CH_3	D	18	$C_{19}H_{19}ClN_2O_3$	155–166	C, H, Cl, N	>1000
4d	CH	C_2H_5	4-FC_6H_4	C_6H_5	–	17	$C_{26}H_{24}FNO_3$	53–55	C, H, F, N	3
4i	CH	*i*-C_3H_7	4-FC_6H_4	C_6H_5	–	22	$C_{27}H_{26}FNO_3$	oil	C, H, F, N	19
4r	N	CH_3	4-FC_6H_4	CH_3	–	18	$C_{19}H_{21}FN_2O_3$	170–172	C, H, F, N	1000

"(p. 53, Table I)

(16c) "In general, the connection between the constitution and the activity of pyrimidine (2r-w) is equal to that of pyridines (2a-q) (for example, 2i vs. 2v, 2a vs. 2r, and 2j vs. 2w; Table I). Inhibitory power largely depends on the substitution pattern of a hetero-aromatic ring. Our [10 to 12] and other's [7] have recently revealed that substitution in the 2-, 4-, and 6-positions in an aromatic ring in the center brings about strong bioactivity.

However, properly choosing a substituent group can further increase the inhibitory power of the compound by an order of magnitude of three.

Introducing an isopropyl group in the 2-position of the hetero-aromatic ring in the center maximizes the bioactivity of compound 2 (for example, 2i vs. 2o, 2p, 2d, and 2a). It was previously revealed that the polar substituent in the 4-position that is considered to imitate a polar ester portion of mevinolin brings about a compound having high activity [7].

In our series, analogs of 4-(chlorophenyl) and 4-(fluorophenyl) substituents are

inhibitors that are equally strong (for example, 2a vs. 2b, 2r, and 2s). A 4-(methoxyphenyl) or 4-[(trifluoromethyl) phenyl] substituent brings about excessive loss of the activity(2m, and 2n vs. 2i,).

It is known that the substituent in the 6-position is the most important for the most appropriate bioactivity. A remarkable increase in titer can be obtained not only by introducing a bulky alkyl group (for example, 2f, 2g, 2h vs. 2e, and 2s) but also by using a phenyl portion (for example, 2i, 2j, 2k, 2v, and 2w)." (p. 55, the right column, ll. 9 to 30)

(16d) "Different from the SAR test 7 in other series, we revealed that a bulky lipophilic substituent group in the 6-position in an aromatic ring in the center contributes greatly to the bioactivity of the synthesized HMG-CoA reductase inhibitors." (p. 57, the right column, ll. 13 to 17)

L Described Matters in Evidence A No. 20

Evidence A No. 20, which had been distributed before the priority date for the Invention, describes the following matters in its Japanese translated sentences:

(20a) "The lipophilicity (log P) and the surface tension of four HMG-CoA reductase of inhibitors, pravastatin, lovastatin, mevastatin, and simvastatin, were measured. The pravastatin had a low log P value and a high surface tension compared with the other three. These physicochemical characteristics may be a cause of tissue-selective uptake of cell cytoplasm exhibited by pravastatin." (p. 117, Abstract)

(20b) "Pravastatin, lovastatin, mevastatin, and simvastatin (FIG. 1) are competitive inhibitors having strong efficacy against 3-hydroxy-3-methylgultarylcoenzyme A (HMG-CoA) reductases. [1, 2)] Among these drugs, pravastatin is distinguished from the other three agents in terms of selective control of cholesterol synthesis in the liver. The tissue selectivity of pravastatin may be caused by its property of not being efficiently taken up by the cells other than liver cells. Considering structural differences among these compounds, a hypothesis can be made that relative hydrophobicity caused by a hydroxyl group in the 6-position relates to the tissue selectivity of pravastatin. In order to analyze this vision physicochemically, the partition coefficient and the surface tension of the four HMG-CoA reductase inhibitors were measured for comparison." (p. 117, the left column, l.1 to the right column, l. 8)

(20c) " Result and Discussion

The partition coefficient is one of the most important causes in measuring the efficiency of a flow of a drug in vivo. In Table I, the log P values of four inhibitors are shown in lactone types and sodium salt types. The order of the log P values is;

pravastatin<<mevastatin<lovastatin<simvastatin in either types, [8], showing that pravastatin is more hydrophilic than the others.

It is widely known that log P has an additional structural characteristic relating to organic compounds. While mevastatin had no methyl group in the 6-position in a hexahydro naphthalene ring, lovastatin and simvastatin have a methyl group in the 6-position. In addition, simvastatin has an additional methyl group in a closed chain on a butylester side. Meanwhile, pravastatin has a hydroxyl group in the 6-position. From the viewpoints of a lipophilic influence of the methyl group and a hydrophilic influence of the hydroxyl group, the order of the log P values of the observed HMG-CoA reductase inhibitors can be said to be reasonable." (p. 118, the right column, l. 8 to page. 119, the right column, l. 8)

M Described Matters in Evidence A No. 24

Evidence A No. 24, which had been distributed before the priority date for the Invention, describes the following matters in its Japanese translated sentences:

(24a) "The interest in the influence of reductase-inhibiting agents other than the liver is based on a recent remark to the effect that lovastatin and simvastatin contained in HMG-CoA reductase-inhibiting agents cause cataracts to dogs when administered at a high dose." (p. 1411, the left column, ll.9 to 12)

N Described Matters in Evidence A No. 57

Evidence A No. 57, which had been distributed before the priority date for the Invention, describes the following matters:

(57a) "Thus, if the constitution of an acting component in a natural product is determined, a direction of checking how the action changes with gradual change of the constitution is established. Finding a better pharmacological action in a new product thus made leads to drug development, and even when no pharmacological action is found therein, accumulating to systematize this knowledge establishes 'the relation between chemical constitution and pharmacological action' [3] therein, and will be useful in drug designing to be described later as basic knowledge in developing new drug medicines." (p. 67, ll. 22 to 28)

O Described Matters in Evidence A No. 58

Evidence A No. 58, which had been distributed before the priority date for the Invention, describes the following matters:

(58a) "4. Procedure following molecular conversion manipulation, and possibility of

differentiation from a chemical standpoint.

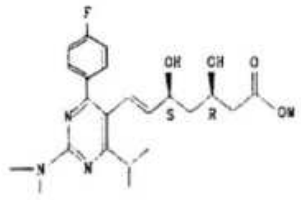
a. Preparation of homologous compounds whose constitutions are varied by degrees. One series of homologous compounds can be obtained by continuously varying their molecular constitutions by degrees. Thus, the physicochemical properties of the chemical drugs vary by degrees, and accordingly the bioactivity could vary by degrees [54, 142] (see Chapter IV). " (p. 80, l. 4 to the last line)

(2) Invention disclosed in Evidence A No. 1 (“A 1 Invention”)

Evidence A No. 1 describes in Example 1 (see summarization 1c) a specific production method for producing

a "(3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methyl-ethy1)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid sodium salt", and

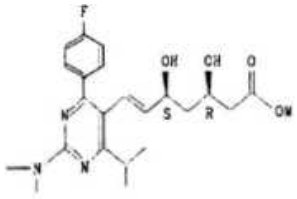
the "(3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methyl- ethy1)-2-(dimethylamino) pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid sodium salt" is a compound expressed by the following chemical formula. "



(M=Na)"

Thus, it can be said that Evidence A No. 1 discloses the invention regarding

"



a compound of (M=Na)" (hereinafter referred to as the "A 1 Invention").

(3) Comparison / Judgment

(3-1) The Invention 1

A Comparison

The invention will be compared with the A 1 Invention.

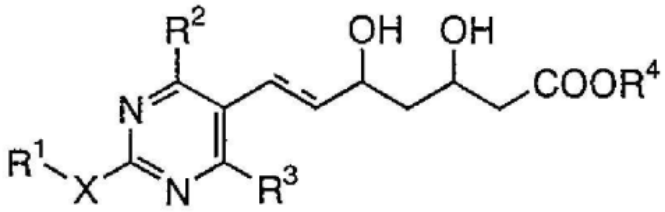
A 1 Invention corresponds, also in "formula (I)" of the Invention 1, to a

compound in which

"R^1" represents "methyl", "R^2" represents "4-fluorophenyl", "R^3" represents "1-methyl- ethyl" (isopropyl), "R^4" represents "Na", "X" represents an imino group substituted with a methyl group; and the "broken lines" indicate presence of a double bond".

Thus, both of the Invention 1 and the A 1 Invention are identical in terms of being a compound comprising one of a compound and its lactone ring closure compound expressed by

"Formula (I):



(where

R^1 represents a low-grade alkyl;

R^2 represents a phenyl substituted with a halogen;

R^3 represents a low-grade alkyl; and

broken lines indicate presence or absence of a double bond.).

And they are different in terms of the following features.

(1-i) Regarding X, it represents an imino group substituted with an alkylsulfonyl group in the Invention 1 while it represents an imino group substituted with a methyl group in the A 1 Invention

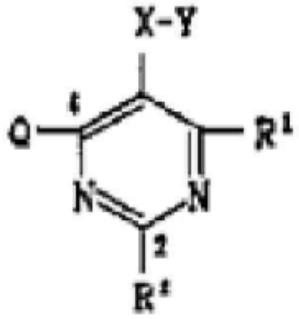
(1-ii) Regarding R^4, it represents a calcium ion that forms one of hydrogen and a hemicalcium salt in the Invention 1 while it represents a sodium ion that forms a sodium salt in the A 1 Invention

B Examination on Different Features

(A) Motivation based on Evidence A No. 1 and Evidence A No. 2

A 1 Invention can be said, in

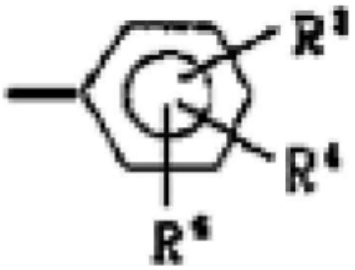
"Formula I, which is described in the scope of claims of Evidence A No. 1,



I

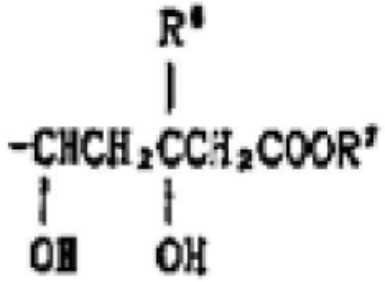
"

selecting "isopropyl" that is "C_{1-6}alkyl not containing an asymmetric carbon" as "R^1",
selecting "methyl" that is "-$N(R^8)_2$, where R^8 independently is C_{1-4}alkyl not containing an asymmetric carbon", and selecting "Q"a" of "Q"" as "Q";
that is, "



"

selecting two "hydrogen" and one "fluoro" among "R^3", "R^4", and "R^5",
selecting "vinylene" as "X", and
selecting "hydrogen" of "R^6" and a "sodium ion" that is a "cation" of "R^7"



" as "Y" (see summarization 1a).

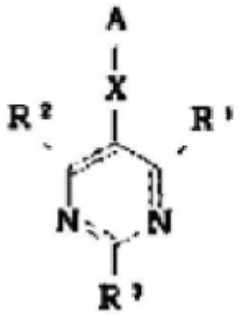
In addition, because the compound of the A 1 Invention was obtained in Example 1b), the data actually show that the compound of A 1 Invention has

pharmacological action to inhibit an "HMG-CoA reductase" (see summarization 1b). While it cannot be said that in the entire range that the compound expressed by formula I described in the scope of claims of Evidence A No. 1 has the pharmacological action like that of the A 1 Invention, the compound expressed by formula I described in the scope of claims of Evidence A No. 1 can be said to have such a pharmacological action as the A 1 Invention .

When the Invention 1 is compared with the Formulae I described in the scope of claims in Evidence A No. 1, the Invention 1 has "-$N(R^8)_2$ as "R^2" and an alkylsulfonyl group (-SO_2R'; R' is an alkyl group) as "R^8". "R^8" is not "methyl" that is "C_{1-4}alkyl not containing an asymmetric carbon" in the A 1 Invention. However, a compound selecting these substituent groups is not included in the range of the above-described formula I.

Accordingly, it cannot be said that the compounds that are not included in formula I of Evidence A No. 1 can be expected to have pharmacological action to inhibit "HMG-CoA reductase activity". Therefore a motivation for substituting the "dimethylamino group" in A 1 Invention by "-$N(CH_3)(SO_2R')$", which is an option that is not included in the range of formula I, cannot be found.

Next, in Evidence A No. 2, in "general formula



(I)

"

It is described that

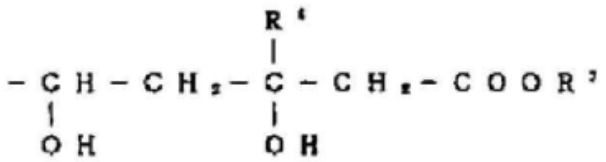
"alkyl" is selected as "R^1",

"aryl" is selected as "R^2",

"alkyl" and "alkylsulfonyl" are selected as "R^4" and "R^5 " in "- NR^4 R^5" as "R^3",

"-CH=CH-" is selected as "X",

"



" is selected as "A", wherein "hydrogen" is selected as "R^6", and
a "cation" is selected as "R^7" as respective options, (see summarization 2a). Further, it is also described that as "particularly preferred compounds of the general formula (I)" are those
in which
" isopropyl " is selected as "R^1",
"phenyl" monosubstituted by "fluorine " is selected as "R^2",
"methyl" and "methylsulfonyl" are selected as "R^4" and "R^5 " in "- NR^4 R^5" as "R^3" as respective options (see summarization 2d), and "calcium cations" are selected as "R^7" as an option (see summarization 2c).

The compound expressed by general formula (I) of Evidence A No. 2 can be an HMG-CoA reductase inhibitor (see summarization 2b), and has a pyrimidine ring as a basic skeleton, and substituent groups in the 2-, 4-, and 6-positions of the pyrimidine ring, similarly and in common with the compound expressed by formula I of Evidence A No. 1. While compounds contained in both of the compounds may partially overlap each other depending on selected substituent groups, the compound expressed by formula (I) of Evidence A No. 1 and the compound expressed by general formula (I) of Evidence A No. 2 do not correspond with each other in all of the options of substituent groups of the above-described pyrimidine rings, and are specified as compounds having different chemical structural formulae, whereby they could be HMG-CoA reductase inhibitors assuming that the compounds are compounds of the chemical structural formulae.

It cannot be said that the compounds have the same HMG-CoA reductase inhibitory action if the constitutions of compounds are different from each other, so that even if "- NR^4 R^5" in "R^3" in the general formula of Evidence A No. 2 corresponds to a generic concept of the dimethylamino group of A 1 Invention, it cannot be said at all that there is a motivation for substituting the dimethylamino group of A 1 Invention by a substituent group that is not disclosed in Evidence A No. 1 based on the description of Evidence A No. 2.

In addition, while "R^1", "R^2", and "R^3" in the compound in general formula (I) of Evidence A No. 2 have a considerable number of options (see summarizations 2a and

2d), the options in which at least "X" and "A" are specifically described in the Examples as having the same constitutions as those of A 1 Invention are only "methyl erythro-(E)-3,5-dihydroxy-7-[2,6-dimethyl-4-(4-fluorophenyl)-pyrimid-5-yl]-hept-6-eno ate" of Example 8 (R^3 is methyl), "methyl erythro-(E)-3,5-dihydroxy-7-[4-(4-fuorophenyl)-6-methyl-2-phenyl-pyrimid-5-yl]-hept-6-enoate" of Example 15 (R^3 is phenyl), and "methyl erythro-(E)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-6-isopropyl-2-phenyl-pyrimid-5-yl]-he pt-6-enoate" of Example 23 (R^3 is phenyl) (see summarizations 2e, 2f, and 2g), and there is no description about a compound in which "- NR^4 R^5" is selected as "R^3". In addition, there is no description about a production method or a pharmacological test for HMG-CoA reductase-inhibiting activity of a compound in which "- NR^4 R^5" is substituted, and thus there is no description about selecting the specific combination of "methyl" and "methylsulfonyl" as "R^4" and "R^5" in "- NR^4 R^5".

Thus, it cannot be said that the compound in which "methyl" and "methylsulfonyl (SO_2CH_3)" are selected as "R^4" and "R^5" in "- NR^4 R^5", which is only a substituent group that could be selected from a considerable number of options as "R^3" in general formula (I) described in Evidence A No. 2, is described with technical evidence, and thus it cannot be said that there is a motivation for substituting the "dimethylamino group" in the A 1 Invention by "-N(CH_3) (SO_2CH_3)" based on this description.

(B) Motivation based on Common General Technical Knowledge

Evidence A No. 10 and Evidence A No. 11 disclose that most of cholesterol is synthesized in the liver (see summarizations10a and 11a). Evidence A No. 11 and Evidence A No. 14 disclose that HMG-CoA reductase catalyzes the reaction to biosynthesize cholesterol (see summarizations 10b and 14a), and that HMG-CoA reductase inhibitors inhibit cholesterol biosynthesis (see summarization 14a).

Evidence A No. 7 discloses that "there has been considerable controversy regarding whether confining HMGR inhibitors' action to the liver could reduce the incidence of adverse reactions" (see summarization 7b). Actually, Evidence A No. 24 shows that HMG-CoA reductase inhibitors might cause cataract in dogs (see summarization 24a).

According to these descriptions, because most of cholesterol is synthesized in the liver and HMG-CoA reductase inhibitors inhibit cholesterol biosynthesis, to try to obtain HMG-CoA reductase inhibitors showing higher liver selectivity while taking the adverse reactions into consideration could have been recognized as a technical problem

to be solved at the time of the priority date for the Invention by a person skilled in the art.

Next, Evidence A No. 7 is a research paper about "Relationship between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase" (see summarization 7a), examines the hypothesis that "tissue selectivity is influenced primarily by the relative lipophilicity of the drugs, with the relatively more hydrophilic compounds showing higher liver selectivity" (see summarization 7b), and describes that "abilities of the compounds to inhibit microsome HMGR in vitro that become 'HMG-CoA reductase-inhibiting agents' such as 'lovastatin and pravastatin' were examined", "as evaluation to compare the effects on the liver with the effects on periphery, effects of the compounds on the uptake of [^{14}C] acetate salts in sterol were measured in the tissue cubes derived from rat liver, spleen, and testis", "lipophilicity is an important factor", the ""threshold point" at which the selectivity becomes equal in liver tissues and other tissues is CLOGP=2", while there are exceptions, "when the threshold point is below this value, the compounds are very selective with respect to liver tissues, and when the threshold point is above this value, the compounds are very selective with respect to peripheral tissues" (see summarizations 7c, 7d, and 7e).

Evidence A No. 20 discloses that the lipophilicity (log P) of four HMG-CoA reductase inhibitors, pravastatin, lovastatin, mevastatin, and simvastatin were measured, and the pravastatin had a low log P value, and this physicochemical characteristic may be a cause of tissue-selective uptake of cell cytoplasm (see summarization 20a), and that pravastatin is not effectively taken up in the cells other than liver cells, and its tissue selectivity is due to the hydroxyl group in the 6-position in a hexahydro naphthalene ring (see summarizations 20b and 20c).

Thus, according to the descriptions in Evidence A No. 7 and Evidence A No. 20, although there might be exceptions, it is shown that a hydrophilic compound could increase the liver selectivity among HMG-CoA reductase inhibitors. Thus, a person skilled in the art could have recognized that, at the time of the priority date for the Invention, there was a motivation for using high hydrophilic compounds (log P of two or less) to obtain HMG-CoA reductase inhibitors showing higher liver selectivity by evaluating compounds showing HMG-CoA reductase-inhibiting activity with an index of hydrophilicity,

While both of Evidence A No. 7 and Evidence A No. 20 describe evaluating the hydrophilicity of compounds showing HMG-CoA reductase-inhibiting activity as described above, there is no description about what chemical constitution the compounds showing HMG-CoA reductase-inhibiting activity should have in order to

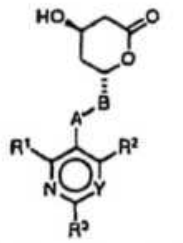
become hydrophilic.

While Evidence A No. 9 discloses that the log P values of the intended compounds can be computed theoretically, and that πx values corresponding to a specific group are indicated, whereby the relative lipophilicity of compounds to be synthesized can be predicted (see summarization 9b), that in aromatic substituents in which R and X are substituent groups, the πx value where X is "3-SO_2CH_3" (a methylsulfonic group) is -1.26 (see summarization 9a), but does not describe a compound conversion means for converting a methyl group into a methylsulfonic group in order to make the compound hydrophilic. The methylsulfonic group described in Evidence A No. 9 is directly substituted by an aromatic ring, and is different in constitution from the Invention 1 in which the pyrimidine ring is substituted by an imino group (containing -N(CH_3) (SO_2CH_3)) substituted by an alkylsulfonyl group.

Thus, while there is a motivation for measuring the hydrophilicity of compounds that have been already known of having HMG-CoA reductase-inhibiting activity, and selecting high hydrophilic compounds among them, it is not known as to whether the compounds always have HMG-CoA reductase-inhibiting activity if a specific substituent group of the A 1 Invention is substituted by another substituent group. Thus, it cannot be said that there is a motivation for substituting the specific substituent group by a methylsulfonyl group in order to make the compounds hydrophilic only based on the fact that compounds having a methylsulfonyl group have small log P values (become hydrophilic).

In addition, while it can be said that gradually varying the constitutions of compounds having a specific pharmacological action to check their actions is generally carried out in developing medicinal compounds (see summarizations 57a and 58a), it is unknown what kind of change will happen in the pharmacological action by the varied chemical constitutions. Thus, in order to convert the chemical constitution of the A 1 Invention to obtain a compound that becomes a hydrophilic HMG-CoA reductase inhibitor, it is natural to obtain a compound that becomes hydrophilic within a range where at least HMG-CoA reductase-inhibiting activity is maintained.

Evidence A No. 16 is a research paper on synthesizing lactones of pyridine- and pyridine-substituted 3,5-dihydroxy-6-heptenoic acid, and studying the connection between the constitution and the activity about the inhibiting activity against HMG-CoA (see summarization 16a), wherein the following constitutional formula "



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

(Y=N)" (note that hereinafter the substitution position to a pyrimidine ring will be described for convenience assuming that -X-R^1 of formula (I) in the Invention 1 corresponds to the 2-position, -R^2 corresponds to the 4-position, and -R^3 corresponds to the 6-position (R^3 in Evidence A No. 16 corresponds to the 2-position, R^2 corresponds to the 4-position, and R^1 corresponds to the 4-position), not based on the description of Evidence A No. 16), discloses that the substitution in 2-, 4-, and 6-positions in an aromatic ring (a pyrimidine ring) in the center brings about strong bioactivity (see summarizations 16b and 16c), that introducing an isopropyl group in the 6-position (R^1) maximizes the bioactivity, that 4-(chlorophenyl) and 4-(fluorophenyl) substituents of the polar substituents in the 4-position (R^2) are strong inhibitors, and that the substituent in the 2-position (R^3) is the most important for the most appropriate bioactivity, and a remarkable increase in titer can be obtained not only by introducing a bulky alkyl group but also by using a phenyl portion (see summarization 16c).

Thus, it cannot be said that a person skilled in the art who had read the description of Evidence A No. 16 was motivated to substitute the "R^2" of Formula I of Evidence A No. 1 with "-N(CH_3)(SO_2R')" that is not described in Evidence A No. 1 or Evidence A No. 16 while the "dimethylamino group" in A 1 Invention might be substituted by an alkyl group or a phenyl ring by combining the feature that a bulky alkyl group or a phenyl ring in the substituent in the 2-position of the compound in which the 6-position of the pyrimidine ring is substituted by an isopropyl group and the 4-position is substituted by a 4-fluorophenyl group, which is similar to the A 1 Invention, indicate strong inhibiting activity, and the feature that "$C_{1\text{-}6}$alkyl not containing an asymmetric carbon atom" can be selected as the "R^2" of Formula I of Evidence A No. 1 (see summarization 1a). In addition, as described above in (A), it cannot be said that "-N(CH_3) (SO_2CH_3)" is selected based on the description of Evidence A No. 2 that is not related to Evidence A No. 1 or Evidence A No. 16. Evidence A No. 16 discloses the bulky lipophilic substituent group in the 2-position in an aromatic ring in the center contributes greatly to the bioactivity of the synthesized HMG-CoA reductase inhibitors (see summarization 16d), so that any indication about a substituent group or a

substitution position to make A 1 Invention hydrophilic is not acknowledged therein.

While Evidence A No. 29 discloses search results of a compound having a methylsulfonyl group as a substituent group that had been already present before the priority date for the Invention, and Evidence A No. 30 discloses a compound having a methylsulfonyl group as a substituent group, it is unknown whether the compounds are HMG-CoA reductase inhibitors, and there is no description about what properties the compounds would have when they had a methylsulfonyl group as a substituent group. Thus, converting the dimethylamino group A 1 Invention to substitute the methyl group by a methylsulfonyl group cannot be easily conceived only because a compound having a methylsulfonyl group as a substituent group had been already present before the priority date for the Invention.

Other evidences distributed before the priority date for the Invention does not teach technical meaning for substituting a methyl group by a methylsulfonyl group. As a result, there is no motivation for substituting the "dimethylamino group" in the 2-position in A 1 Invention by "-N(CH_3)(SO_2R')" for hydrophilization of the compound of the A 1 Invention.

Thus, even if a person skilled in the art could have arrived at converting the chemical constitution of A 1 Invention to obtain a hydrophilic compound, it cannot be said that there is a motivation for substituting only a methyl group, which is one of "dimethylamino groups" in a specific position (the 2-position in a pyrimidine ring), by a methylsulfonyl group (an alkylsulfonyl group) and selecting "-N(CH_3)(SO_2R')" for hydrophilization of the compound of the A 1 Invention.

(C) Summary

Therefore, because it cannot be said that applying the constitution of the different feature (1-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, there is no need to discuss the different feature (1-ii), and thus it cannot be said that the Invention 1 could have been easily made by a person skilled in the art based on the descriptions of A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

C Effect of the Invention 1

While it cannot be said that the Invention 1 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention as described above in item B, the effect will be discussed just to make

sure.

It is acknowledged that the effect of the Invention 1 is to provide an effective compound that becomes a drug showing strong HMG-CoA reductase-inhibiting activity (see paragraph [0042] in the Description of the Patent). The Description of the Patent shows that not a free acid or a hemicalcium salt of the Invention 1 but a sodium salt indicated by the compound (Ia-1) has specifically a pharmacological effect of HMG-CoA reductase-inhibiting activity stronger than that of mevinolin Na. Considering the action mechanism that inhibition of HMG-CoA reductase activity is generated by the interaction of steric constitution between the enzyme and the compound becoming an inhibitor, it is natural to consider that those compounds work equally on the enzyme regardless of the forms of salts in vivo. A free acid or a hemicalcium salt, even when used for a sodium salt, can be assumed to show HMG-CoA reductase-inhibiting activity in the same manner. According to Evidence A No. 3, "S-4522", which is a hemicalcium salt, actually shows stronger HMG-CoA reductase-inhibiting activity than mevinolin Na (see summarizations 3a and 3b), which supports that the above assumption is correct.

Meanwhile, Evidence A No. 1 discloses that the compound of the A 1 Invention shows HMG-CoA reductase-inhibiting activity (see summarization 1b), but does not disclose that what will happen to HMG-CoA reductase-inhibiting activity when the "dimethylamino group" in the 2-position of the pyrimidine ring is substituted by "-N(CH_3) (SO_2CH_3)" that is not included in the range of formula I in the A 1 Invention. Evidence A No. 1 discloses a compound in which the 2-position of the pyrimidine ring is substituted by "4-morpholinyl group", but in this compound as well, "-N(R^8)2" is selected as the "R^2" in Formula I of Evidence A No. 1, and the "R^8" is selected from "both R^8 together with the nitrogen atom forming part of a 5-,6- or 7-membered optionally substituted ring optionally containing one or more further heteroatoms (ring B)" as defined. Thus, Evidence A No. 1 does not disclose that what will happen to the activity when "-N(CH_3) (SO_2CH_3)" that is not included in the range of formula I is used as the "R^2" substitutes.

Next, while Evidence A No. 2 discloses selecting "-NR^4R^5" as "R^3" and selecting methyl and methylsulfonyl as options of "R^4" and "R^5" in formula I as described above, there is no description that the methyl group and the methylsulfonyl group are equivalent substituent groups in terms of pharmacological action, and there is even no description of an example of a compound in which "-NR^4R^5" is selected as "R^3". Thus, what pharmacological action can be obtained by this compound cannot be predicted from the description of Evidence A No. 2.

Further, while Evidence A No. 16 discloses a compound having an isopropyl group in the 6-position and a 4-fluorophenyl group in the 4-position of the pyrimidine ring, which is similar to the compound of the Invention 1, the 2-position is substituted by an alkyl group or a phenyl group, and there is no description of "-N(CH_3) (SO_2CH_3)". It cannot be said that the same activity can be obtained by a compound having any substituent group in the 2-position only if the compound has an isopropyl group in the 6-position and a 4-fluorophenyl group in the 4-position.

The pharmacological action of the compound closely relates to the constitution of the compound. When the substituent group of a compound having pharmacological action is varied, the pharmacological action of the compound accordingly varies, and in some cases pharmacological action that was obtained up to the time could no longer be obtained. Thus, even taking into consideration not only Evidences A Nos.1, 2, 16, but also the descriptions of the other evidences, it cannot be said that a person skilled in the art could predict that what will happen to the HMG-CoA reductase-inhibiting activity of the compound of the A 1 Invention in which the "dimethylamino group" in the 2-position of the pyrimidine ring is substituted by "-N(CH_3) (SO_2CH_3)".

Meanwhile, Evidence A No. 3 is a demandee's internal document concerning a summary of test results carried by the demandee. Because there was a contradiction between the HMG-CoA reductase-inhibiting activity of "SDZ-65129" of the A 1 Invention and that of "S-4522" in the Invention 1 reported during the examination procedure, a comparison was made under the same conditions between mevinolin Na (ring-opening), mevinolin (lactone body), SDZ-65129, and S-4522 in terms of the HMG-CoA reductase-inhibiting activity, and test results of the comparison are shown in Evidence A No. 3 (see summarizations 3a and 3b). The Description of the Patent specifically describes the HMG-CoA reductase-inhibiting activity of a sodium salt as described above, which is not a compound of the Invention 1, so that even a free acid or a calcium salt can be understood to show HMG-CoA reductase-inhibiting activity in the same manner from the viewpoint of the pharmacological action mechanism. Thus, the results shown in Evidence A No. 3 can be taken into consideration as evidence to support the correctness of the understanding.

The HMG-CoA reductase-inhibiting activity (IC_{50} value) of S-4522 indicated in Evidence A No. 3 is 14±3nM, and the HMG-CoA reductase-inhibiting activity (IC_{50} value) of Mevinolin Na (ring-opening) is 28±9nM. Thus, considering that the calcium salt of the Invention 1 has activity two times as strong as that of Mevinolin Na, and that the IC_{50} value shown therein indicates average±standard errors (see summarization 3b),

it can be said that the compound of the Invention 1 will have HMG-CoA reductase inhibitory action stronger than that of Mevinolin Na, even while taking the standard errors into consideration when the compound of the Invention 1 and Mevinolin Na are examined under the same conditions. Note that according to the description of Evidence A No. 5 (see summarization 5a), which is a summary Q & A between the patentee and the supporting intervener (ZENECA), the average value of the IC_{50} values of measurement 1 to measurement 3 is consistent with the IC_{50} value of Evidence A No. 3, and the measurements were carried out around the same time frame, and thus, it can be understood that the IC_{50} value indicated in Evidence A No. 3 is a value described as an average of the results of a plurality of measurements, and as falling within a range of variability of the measurement errors.

Thus, the pharmacological action that the HMG-CoA reductase-inhibiting activity of the Invention 1 is stronger than that of Mevinolin Na can be assumed according to the Description of the Patent, and is also supported by Evidence A No. 3. Thus, the effect of the Invention 1 cannot be denied.

D Summary

As described above, it cannot be said that the Invention 1 could have been easily made by a person skilled in the art based on the invention disclosed in Evidence A No. 1 (the main Cited Document) and the invention disclosed in Evidence A No. 2, which were distributed before the present application (the priority date), and the common general technical knowledge at the time of the priority date for the Invention.

(3-2) The Invention 2

A Comparison

The invention 2 will be compared with the A 1 Invention.

The A 1 Invention is a "(3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methyl-ethyl)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid sodium salt". Thus, the Invention 2 and A 1 Invention are identical in terms of being "7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-substituentamino pyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" and are different in terms of the following features;

(2-i) The feature that the N-substituent group of the N-methyl-N-substituent amino group in the 2-position of pyrimidine is a methylsulfonyl group in the Invention 2, while the N-substituent group of the N-methyl-N-substituent amino group in the 2-position of pyrimidine is a methyl group in the A 1 Invention

(2-ii) The feature that a free acid is used in the Invention 2, while a sodium salt is used

in the A 1 Invention
(2-iii) The feature that the optical rotation is dextrorotation (+) in the Invention 2, while the optical rotation is unknown in the A 1 Invention

B Examination on Different Features

The different feature (2-i) is rewritten in accordance with the above-described different feature (1-i), where X represents an imino group substituted by a methylsulfonyl group in the Invention 2, while X represents an imino group substituted by a methyl group in the A 1 Invention. Thus, the compound in the Invention 2 corresponds to a compound in which the "alkylsulfonyl group" is limited to a "methylsulfonyl group" in the different feature (1-i).

As described above in item (3-1) B, because it cannot be said that applying the constitution of the different feature (1-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, it cannot be either said that applying the constitution of the further-limited different feature (2-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different features. Thus, it cannot be said that the Invention 2 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(3-3) The Invention 5
A Comparison

The chemical structural formula in "formula (I)" of the Invention 5 is the same as the chemical structural formula in "formula (I)" of the Invention 1, so that as described above in item (3-1) A,

The A 1 Invention corresponds, also in "formula (I)" of the Invention 5, to a compound in which

"R^1" represents "methyl", "R^2" represents "4-fluorophenyl", "R^3" represents "1-methyl-ethyl" (isopropyl), "R^4" represents "Na", "X" represents an imino group substituted with a methyl group; and the "broken lines" indicate presence of a double bond.

Thus, the Invention 5 and the A 1 Invention are identical in terms of being a "compound expressed by
Formula (I):
(being the same as the formula (I) in claim 1, the chemical formula is omitted.)

(where
R^1 represents a low-grade alkyl;
R^2 represents a phenyl substituted with a halogen;
R^3 represents a low-grade alkyl; and
broken lines indicate presence or absence of a double bond"
while being different in terms of the following features.
(5-i) The feature that X represents an imino group substituted with a methylsulfonyl group in the Invention 5, while X represents an imino group substituted with a methyl group in the A 1 Invention
(5-ii) The feature that R^4 represents a calcium ion that forms a hemicalcium salt in the Invention 5, while R^4 represents a sodium ion that forms a sodium salt in the A 1 Invention.

B Examination on Different Features

The different feature (5-i) corresponds to a compound in which the "alkylsulfonyl group" is limited to a "methylsulfonyl group" in the different feature (1-i).

As described above in item (3-1) B, because it cannot be said that applying the constitution of the different feature (1-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, it also cannot either said that applying the constitution of the further-limited different feature (5-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different feature. Thus, it cannot be said that the Invention 5 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(3-4) The Invention 9

A Comparison

The chemical structural formula in "formula (I)" of the Invention 9 is the same as the chemical structural formula in "formula (I)" of the Invention 1, so that as described above in item (3-1) A,
the A 1 Invention corresponds, also in "formula (I)" of the Invention 9, to a compound in which

"R^1" represents "methyl", "R^2" represents "4-fluorophenyl", "R^3" represents "1-methyl-ethyl" (isopropyl), "R^4" represents "Na", "X" represents an imino group

replaced with a methyl group; and the "broken lines" indicate presence of a double bond.

Thus, the Invention 9 and the A 1 Invention are identical in terms of being a "compound expressed by
Formula (I):
(being the same as the formula (I) in claim 1, the chemical formula is omitted.)
(where
R^1 represents a low-grade alkyl;
R^2 represents a phenyl substituted with a halogen;
R^3 represents a low-grade alkyl; and
broken lines indicate presence of a double bond"
while being different in terms of the following features.
(9-i) The feature that X represents an imino group substituted with a methylsulfonyl group in the Invention 9 while X represents an imino group substituted with a methyl group in the A 1 Invention
(9-ii) The feature that R^4 represents a calcium ion that forms a hemicalcium salt in the Invention 9, while R^4 represents a sodium ion that forms a sodium salt in the A 1 Invention

B Examination on Different Features

The different feature (9-i) corresponds to a compound in which the "alkylsulfonyl group" is limited to a "methylsulfonyl group" in the different feature (1-i).

As described above in item (3-1) B, because it cannot be said that applying the constitution of the different feature (1-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, it also cannot be said that applying the constitution of the further-limited different feature (9-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different feature. Thus, it cannot be said that the Invention 9 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(3-5) The Invention 10
A Comparison

The chemical structural formula in "formula (I)" of the Invention 10 is the

same as the chemical structural formula in "formula (I)" of the Invention 1 except that the asymmetric carbon atom (C*) is indicated, so that as described above in item (3-1) A,

The A 1 Invention corresponds, in "formula (I)" of the Invention 10, to a compound in which

"R^1" represents "methyl", "R^2" represents "4-fluorophenyl", "R^3" represents "1-methyl-ethyl" (isopropyl), "R^4" represents "Na", "X" represents an imino group substituted with a methyl group; the "broken lines" indicate presence of a double bond; and C* represents the optically active substance of an asymmetric carbon atom.

Thus, the Invention 10 and the A 1 Invention are identical in terms of being an "optically active compound expressed by

Formula (I):

(being the same as the formula (I) in claim 1, the chemical formula is omitted.)

(where

R^1 represents a low-grade alkyl;

R^2 represents a phenyl substituted with halogen;

R^3 represents a low-grade alkyl; and

broken lines indicate presence of a double bond; and

C* represents an asymmetric carbon atom"

while being different in terms of the following features.

(10-i) The feature that X represents an imino group substituted with an alkylsulfonyl group in the Invention 10, while X represents an imino group substituted with a methyl group in the A 1 Invention

(10-ii) The feature that R^4 represents a calcium ion that forms a hemicalcium salt in the Invention 10, while R^4 represents a sodium ion that forms a sodium salt in the A 1 Invention

(10-iii) The feature that the optically active substance is obtained by a "method comprising the steps of: reacting a compound expressed by formula (b) with a (3R)-3-(tert-butyldimethylsilyloxy-5-oxo-6-triphenyl) phosphoranyliden hexanoic acid derivative to produce a compound expressed by formula (c);

(being the same as the above-described formula (b), the chemical formula is omitted.)

(being the same as the above-described formula (c), the chemical formula is omitted.)

producing a compound expressed by formula (d) by separating the tert-butyldimethylsilyl group from the compound expressed by formula (c); and reducing the compound expressed by formula (d) (being the same as the above-described formula (d), the chemical formula is omitted.) in the Invention 10

while the compound is not obtained in the manner like this in the A 1 Invention

B Examination on Different Features

The different feature (10-i) is substantially the same as the different feature (1-i). Thus, as described above in item (3-1) B, it cannot be said that applying the constitution of the different feature (10-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different features. Thus, it cannot be said that the Invention 10 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(3-6) The Invention 11

A Comparison

The invention 11 will be compared with the A 1 Invention.

A 11 Invention is a "(3R,5S)-[E]-7-[4-(4-fluorophenyl)-6-(1-methyl-ethyl)-2-(dimethylamino)pyrimidine-5-yl]-3,5-dihydroxy-6-heptenoic acid sodium salt. Thus, the Invention 11 and A 1 Invention are identical in terms of being "7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-substituentamino pyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid salt" and are different in terms of the following features;

(11-i) The feature that the N-substituent group of the N-methyl-N-substituent amino group in the 2-position of pyrimidine is a methylsulfonyl group in the Invention 11, while the N-substituent group of the N-methyl-N-substituent amino group in the 2-position of pyrimidine is a methyl group in the A 1 Invention

(11-ii) The feature that a calcium salt is used as a salt in the Invention 11, while a sodium salt is used as a salt in the A 1 Invention

(11-iii) The feature that the optical rotation is dextrorotation (+) in the Invention 11, while the optical rotation is unknown in the A 1 Invention

B Examination on Different Features

The different feature (11-i) is rewritten in accordance with the above-described different feature (1-i), where X represents an imino group substituted by a methylsulfonyl group in the Invention 11, while X represents an imino group substituted by a methyl group in the A 1 Invention. Thus, the compound in the Invention 11 corresponds to a compound in which the "alkylsulfonyl group" is limited to a

"methylsulfonyl group" in the different feature (1-i).

As described above in item (3-1) B, because it cannot be said that applying the constitution of the different feature (1-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, it also cannot be said that applying the constitution of the further-limited different feature (11-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different features. Thus, it cannot be said that the Invention 11 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(3-7) The Invention 12

A Comparison

The Invention 12 is "an HMG-CoA reductase inhibitor comprising the compound according to claim 1 as an active ingredient", so that as described above in item (3-1) A, the Invention 12 and the A 1 Invention are identical in terms of being "a compound comprising one of a compound and its lactone ring closure compound expressed by formula (I):

(being the same as the above-described formula (I), the chemical formula is omitted.)

(where

R^1 represents a low-grade alkyl;

R^2 represents a phenyl substituted with a halogen;

R^3 represents a low-grade alkyl; and

broken lines indicate presence or absence of a double bond"

while being different in terms of the following features.

(12-i) The feature that X represents an imino group substituted with an alkylsulfonyl group in the Invention 12, while X represents an imino group substituted with a methyl group in the A 1 Invention

(12-ii) The feature that R^4 represents a calcium ion that forms one of hydrogen and a hemicalcium salt in the Invention 12, while R^4 represents a sodium ion that forms a sodium salt in the A 1 Invention

(12-iii) The feature that the Invention 12 is an HMG-CoA reductase inhibitor comprising the compound according to claim 1 as an active ingredient, while the A 1 Invention is not an agent comprising the compound according to claim 1 as an active ingredient.

B Examination on Different Features

The different feature (12-i) is substantially the same as the different feature (1-i). Thus, as described above in item (3-1) B, it cannot be said that applying the constitution of the different feature (12-i) to the A 1 Invention could have been easily conceived by a person skilled in the art, and there is no need to discuss the other different features. Thus, it cannot be said that the Invention 12 could have been easily made by a person skilled in the art based on the descriptions of the A 1 Invention and Evidence A No. 2 and the common general technical knowledge at the time of the priority date for the Invention.

(4) Allegation of the demandant

A Outline of the allegation of the demandant

(A) Motivation (p. 57, the 13th line from the bottom to p. 59, l. 10 in the written demand for trial, p. 31, l. 11 to p. 32, the last line, and p. 34, l. 7 to p. 37, l. 30 in the written refutation of the trial case, p. 17, the 14th line from the bottom to p. 23, l. 13 in the written statement dated March 24, 2016, and p. 3, l. 27 to p. 11, l. 12 in the oral proceedings statement brief)

It had been a well-known problem before the priority date for the Invention to increase liver selectivity in order to avoid the incidence of adverse reactions accompanied by tissue migration that is non-specific to HMG-CoA reductase inhibitors, and attention had been paid to increasing the hydrophilicity of HMG-CoA reductase inhibitors as means for increasing the liver selectivity. Thus, it can be said that a person skilled in the art could have been sufficiently motivated to derive A 1 Invention as a leading compound to create a compound that is relatively hydrophilic.

It had been well-known that in the compound of the HMG-CoA reductase inhibitor of a pyrimidine ring system of A 1 Invention, the hydroxy heptenoic acid in the 5-position, the para-fluorophenyl group in the 4-position, and the isopropyl group in the 6-position in the pyrimidine ring are important for its activity, so that these positions are not suitable to be substituted (Evidences A Nos. 1 to 8, 10, 16, 25, and 26,), and thus it was inevitable to substitute the dimethylamino group in the 2-position of the pyrimidine ring in terms of the chemical constitution.

That is, Evidence A No. 16 discloses that high inhibiting activity is obtained when the 4-position and the 6-position in the pyrimidine ring are para-fluorophenyl and isopropyl, respectively, even when the substituent group in the 2-position is different, and the different feature of Evidence A No. 16 from A 1 Invention is only the substituent group in the 2-position. Thus, the substitution to make a compound hydrophilic while

maintaining the inhibiting activity that a person skilled in the art who started from the A 1 Invention can conceive must be only substitution in the 2-position of the pyrimidine ring. This can be supported by the feature of a statin compound that has a pyrrole ring and a benzene ring in addition to a pyrimidine ring, as a skeleton, where the hydroxy heptenoic acid, the para-fluorophenyl group, and the isopropyl group are placed in a similar manner (Evidences A Nos. 26, 27, and 44). In addition, the dimethylamino group that is a substituent group in the 2-position of the pyrimidine ring of A 1 Invention can be understood to have higher activity than the bulky lipophilic group although being more hydrophilic than the bulky lipophilic group that is described as a preferable group in Evidence A No. 16, so that the substituent group in the 2-position of the pyrimidine ring that is a lipophilic group in Evidence A No. 16 does not become a disincentive about making A 1 Invention hydrophilic.

When converting the compound of the A 1 Invention, a person skilled in the art takes into consideration the descriptions of Evidence A No. 2 about an HMG-CoA reductase inhibitor expressed by a general formula that includes the compound of the A 1 Invention, and about the substituent amino group in a position corresponding to a substituent group in the 2-position, and focuses attention on the $-NR^4R^5$ that is the only generic concept of the dimethylamino group described as a "particularly preferred compound", and selects acyl, alkylsulfonyl, or arylsulfonyl that is a hydrophilic group among six options of alkyl, aryl, aralkyl, acyl, alkylsulfonyl, and arylsulfonyl in R^4 and R^5.

In the common general technical knowledge, the conversion is made so as not to greatly change the constitution of the compound in order to maintain the activity, and it is natural to substitute only one methyl group of the dimethylamino group, and it is obvious to select the most hydrophilic methylsulfonyl group that can greatly vary the hydrophobicity from the methyl group without selecting arylsulfonyl that varies greatly in steric constitution based on the common general technical knowledge (Evidence A No. 56).

(B) Effect (P. 59, l. 11 to P. 67, l. 6 in the written demand for trial, P. 37, l. 31 to P. 40, l. 19 in the written refutation of the trial case, and P. 11, l. 13 to P.15, l. 5 in the oral proceedings statement brief)

Because Evidence A No. 1 discloses that the compound of the A 1 Invention in which the dimethylamino group in the 2-position of the pyrimidine ring is substituted shows strong HMG-CoA reductase-inhibiting activity, and that a compound in which the dimethylamino group is substituted by a bulky 4-morpholinyl group is a particularly

preferred compound (Example 2b), the compound in which the dimethylamino group is substituted by a bulky morpholinyl group can be understood to demonstrate the same activity. Thus, it can be reasonably predicted that a compound in which the methyl group of the dimethylamino group is substituted by a methylsulfonyl group that is more bulky than the methyl group can maintain its activity.

In addition, because Evidence A No. 2 discloses that compounds having a substituent pyrimidine ring having an amino group substituted by a methylsulfonyl group in the 2-position of the pyrimidine ring are particularly preferred, and those compounds indicate preferable HMG-CoA reductase inhibitory action, it can be reasonably predicted that the compound of A 1 Invention in which the dimethylamino group in the 2-position of the pyrimidine ring is substituted by the methylsulfonyl group indicates preferable HMG-CoA reductase inhibitory action.

The compound of the Invention 1 was granted a patent by alleging that the compound of the Invention 1 indicates HMG-CoA reductase-inhibiting activity nine times stronger than that of the compound of the A 1 Invention in the course of the examination (Evidence A No. 6). According to the results of reliable Evidences A Nos. 3 to 5, although it is not permitted to add data other than the descriptions in the Description of the Patent, the difference is about two times, and the test systems can be understood to vary widely. Thus, even if there is an about two-time difference between the IC_{50} values of the two compounds, the difference cannot be said to be objectively significant (Evidences A Nos. 31 and 32), and it cannot be said that the compound of the Invention has a prominent effect.

In addition, since the compound of the Invention was granted a patent by the dishonest correspondence of Evidence A No. 6 to intentionally show the effect of the Invention better than the actual effect as described above, the data should not be taken into consideration, and the process for establishment of the Patent shows that the demandee admits that the activity of the Invention, which is two times stronger than the activity of the A 1 Invention, has no prominent effect.

The description of the Invention describes that the compound of the example shows HMG-CoA reductase-inhibiting activity that is 4.4 times stronger than that of Mevinolin. However, since the A 1 Invention shows activity about 13.5 times stronger than that of mevinolin, and Evidence A No. 16 indicates that the compounds (2t, 2u, 2y, and 2w) having the skeleton common to the Invention 1 except the substituent group in the 2-position in the pyrimidine ring have relative activity that is stronger (two to eight times) than that of mevinolin, the compound could be predicted to have activity

sufficiently stronger than that of mevinolin by introducing a hydrophilic group in the 2-position in the pyrimidine ring, and could be predicted to have activity maintained or increased up to about three times even if the substituent group in the 2-position in the pyrimidine ring is relatively bulky, considering the comparison between compound 2t and compounds 2u, 2v, and 2w. Thus, even if the methyl group in the dimethylamino group of the A 1 Invention is substituted by a bulky methylsulfonyl group, the difference in activity of this degree could be easily predicted. This can be supported also by the description in Evidence A No. 44 describing that a statin-based HMG-CoA reductase inhibitor having a methylsulfonyl group has activity four times stronger than that of Mevinolin Na.

Further, Table 4 in the description of the Invention has no description of indexes that indicate the measurement numbers and variations, and the test system of the HMG-CoA reductase-inhibiting activity varies widely, where not only IC_{50} values vary but also the strength/weakness of the activity could reverse also in the same test (Evidences A No. 7, 8, and 31), so that it cannot be understood that the Invention 1 has HMG-CoA reductase-inhibiting activity more excellent even than that of mevinolin.

B Examination on the allegation of the demandant

(A) Motivation

As described in (3) (3-1) B. (B), even if there is a motivation for selecting a compound that has higher hydrophilicity among compounds assumed to have HMG-CoA reductase-inhibiting activity, it is unknown whether the compound always keeps the HMG-CoA reductase-inhibiting activity if a specific substituent group in A 1 Invention is substituted by another substituent group. Thus, even if a person skilled in the art could understand that the log P value of the compound having a methylsulfonyl group is reduced (the compound becomes more hydrophilic), it cannot be said that there is a motivation for substituting the specific substituent group in the A 1 Invention by a methylsulfonyl group in order to make the compound hydrophilic.

Because if the A 1 Invention is converted into a hydrophilic compound, at least the converted compound must have MG-CoA reductase-inhibiting activity, it does not mean that a part of a substituent group of A 1 Invention should be substituted by a substituent group that brings about some hydrophilicity, but the substitution needs not influence the HMG-CoA reductase-inhibiting activity.

As described in (3) (3-1) B. (B), even if a person skilled in the art who has read the description of Evidence 16 understands that the difference in chemical constitution between the A 1 Invention and the compound having the activity of Evidence A No. 16

is the difference of the substituent group in the 2-position, he/she will just understand that the A 1 Invention will have HMG-CoA reductase-inhibiting activity even when the "dimethylamino group" in the A 1 Invention is substituted by an alkyl group or a phenyl ring, because Evidence A No. 16 discloses that all of the substituent groups in the 2-, 4-, and 6-positions influence the inhibiting activity, and that when the substituent group in the 2-position in a compound in which the 6-position of the pyrimidine ring is substituted by an isopropyl group and the 4-position is substituted by a 4-fluorophenyl group, which is similar to the A 1 Invention, is a bulky alkyl group or a phenyl ring, the compound shows strong activity. Thus, it cannot be said that a person skilled in the art can understand that the same activity can be obtained even when the "dimethylamino group" in the A 1 Invention is substituted by a substituent group that is not disclosed in Evidence A No. 1 or Evidence A No. 16.

Evidences A Nos. 26 and 27 disclose that in a statin compound that has a pyrrole ring and a benzene ring that is different from a pyrimidine skeleton, hydroxy heptenoic acid, the para-fluorophenyl group, and the isopropyl group are substituted in a similar manner; however, because the activity of the compound is not determined only by the position of an individual substituent group, but is determined by the constitution of the entire compound, it cannot be said that a person skilled in the art can understand, based on these descriptions, that the same activity can be obtained even when the dimethylamino group in the 2-position in the A 1 Invention is substituted by a substituent group other than a bulky alkyl group or a phenyl ring that is disclosed in Evidence A No. 16. Note that, Evidence A No. 44 is a publication distributed after the priority date for the Invention, and cannot be a ground for the common general technical knowledge at the time of the priority date for the Invention, and thus it cannot be said that a person skilled in the art can understand, based on the description in Evidence A No. 44, that the HMG-CoA reductase-inhibiting activity can be maintained even if what happens to the substituent group in the 2-position in the A 1 Invention, because of the same reasons as in Evidences A Nos. 26 and 27.

Evidence A No. 16 does not disclose what to do with the substituent group in order to make the compound hydrophilic, while Evidence A No. 16 is intended to examine the relation between the chemical constitution and the activity (see summarization 16a), and there is no indication to connect the compound of Evidence A No. 16 with the compound of Evidence A No. 2, as already described in (3) (3-1) B. (B).

Next, while general formula (I) of Evidence A No. 2 includes the A 1 Invention according to the description of Evidence A No. 2 as described in (3) (3-1) B. (A), the A 1 Invention is described as one of examples of a group of compounds expressed by

formula 1 in the scope of claims of Evidence A No. 1, which is expressed by another chemical structural formula, although it might partially overlap formula I of Evidence A No. 2. Further, as described in (3) (3-1) B. (A), $-NR^4R^5$ is described as one of a great many options of "R^3" in the "particularly preferred" compounds of general formula (I) of Evidence A No. 2, and there is no description about an example of such a compound, and there is no description of a production method or pharmacological action of the compound. Thus, it cannot be said that a person skilled in the art could arrive at substituting a specific substituent group of A 1 Invention based on the description in Evidence A No. 2 that is not technically supported.

Evidence A No. 2 showing that $-NR^4R^5$ can be selected as "R^3", and "alkyl" and "alkylsulfonyl" can be selected as "R^4" and "R^5" only means that the selection is conceivable as a possibility among a great many options, and thus it cannot be said that a compound in which the above-described specific options are selected can be specifically recognized from the description in Evidence A No. 2. Thus, it cannot be said that there is a motivation for substituting only one methyl group of the dimethylamino group of the A 1 Invention by an alkylsulfonyl group based on the description in Evidence A No. 2.

In addition, even though it is the common general technical knowledge not to greatly change the constitution of the compound in order to maintain the activity in the conversion of the compound, there is no description about what chemical constitution the compound should have in order to make the compound hydrophilic without the HMG-CoA reductase-inhibiting activity being influenced by the conversion as described above in any of the evidences distributed before the priority date for the Invention. Evidence A No. 56 is a publication distributed after the priority date for the Invention, and cannot be a ground for the common general technical knowledge at the time of the priority date for the Invention at all, and what can be understood from Evidence A No. 56 is only a great difference between the values of π of the methyl group and the methylsulfonyl group, the values of π indicating hydrophobicity (the methylsulfonyl group has a value more hydrophilic than the methyl group), and Evidence A No. 56 cannot be said to indicate substituting only one methyl group of the dimethylamino group of A 1 Invention by a methylsulfonyl group.

Therefore, the allegation of the demandant cannot be accepted.

(B) Effect

As described in (3) (3-1) C, the Invention 1 can be said to provide a specific effect of providing a compound that becomes an effective drug showing strong

HMG-CoA reductase-inhibiting activity based on the description in the Description of the Patent.

A measurement method of the HMG-CoA reductase inhibitory activities described in the Description of the Patent is to mix a mixture of a rat liver microsome solution and a [3-^{14}C]HMG-CoA solution with a test compound to incubate to develop the resulting mixture on thin-layer chromatography plates to scrape the chromatograms whose Rf value was between 0.45 to 0.60 to measure the specific radio-activities of the obtained products based on the assumption that the relative activity of a mevinolin sodium salt as reference drug is 100 (see [0040] to [0041]). Seeing Evidence A No. 7 and Evidence A No. 8 using test methods using a rat liver microsome similarly to the Patent, the IC_{50} of lovastatin (compound 1, mevinolin) is 2.5 times as large as the IC_{50} of fluvastatin (compound 3) in Evidence A No. 7 (see summarization 7b), while the IC_{50} of a lovastatin sodium salt is 1/10 of the IC_{50} of fluvastatin (XU62-320) in Evidence A No. 8 (see summarizations 8c and 8e), and thus there is no agreement between those results. However, test methods using a rat liver microsome are used also in either of Evidence A No. 7 and Evidence A No. 8 (see summarizations 7c, 7d, and 8d). According to Evidence B No.31 (a written opinion by Prof. Ito), it can be understood that the measurement method of HMG-CoA reductase-inhibiting activity described in the Description of the Patent at the time of the priority date for the Invention was a general measurement method of HMG-CoA reductase-inhibiting activity that was ordinarily used. Seeing Table 4 of the Description of the Patent indicating HMG-CoA reductase-inhibiting activity based on the above-described acknowledgement, even if there is no description of indexes that indicate the measurement numbers and variations in Table 4 in the description of the Invention, no description of indexes does not mean that the results of Table 4 are immediately untrustworthy. As long as the Description of the Patent explicitly states that the result that the Invention 1 could obtain higher activity than Mevinolin Na when measured under the same conditions, the effect cannot be denied if there is no specific evidence that the result is wrong.

Whether or not the Invention has a prominent effect should be determined by whether or not the effect of the Invention could be predicted from the A 1 Invention and the common general technical knowledge at the time of the priority date for the Invention, and the Invention need not necessarily have HMG-CoA reductase inhibitory action stronger than that of the A 1 Invention.

It cannot be said that a person skilled in the art could predict whether or not HMG-CoA reductase inhibitory action that is as strong as that of the A 1 Invention could be obtained by substituting only one methyl group of the dimethylamino group of

the A 1 Invention by a methylsulfonyl group so as to form the substituent group of the Invention 1, even taking into consideration Evidence A Nos. 1, 2, and 16, and other evidences as described above in (3) (3-1) C. Note that Evidence A No. 44 is a publication distributed after the priority date for the Invention, and cannot be a ground for the common general technical knowledge at the time of the priority date for the Invention. In addition, the above-described effect cannot be predicted from the descriptions of Evidence A No. 44.

Further, the Invention has an effect that can be assumed from the descriptions in the Description of the Patent even without taking into consideration Evidence A No. 6 submitted in the process for establishment of the Patent, and the effect is supported by Evidence A No. 3, so that the effect of the Invention should not be denied by the patent-obtaining history of the Patent.

Therefore, the allegation of the demandant cannot be accepted.

(5) Summary

As described above, it cannot be said that the Inventions 1, 2, 5, and 9 to 12 could have been provided easily by a person ordinarily skilled in the art before the present application (the priority date) according to the inventions disclosed in Evidence A No. 1 (the main Cited Document) and Evidence A No. 2, which had been distributed before the present application (the priority date), and the common general technical knowledge at the time of the priority date for the Invention.

2 Reason 2 for invalidation

(1) Supporting requirement

Article 36(5) of the Patent Act before revision by the Act of 1994 stipulates that "the statement of the scope of claims as provided in paragraph (3)(iv) shall comply with each of the following items", and stipulates that "the invention for which a patent is sought is stated in the detailed explanation of the invention." in its item (i). Whether or not the description of the scope of claims for patent complies with the requirement stipulated in the item concerned, which is the so-called supporting requirement of the specification, should be determined by examining whether or not the invention described in the scope of claims for patent is the invention described in the detailed description of the invention, and whether or not it can be acknowledged that a person skilled in the art could solve the problems of the invention based on the detailed description of the invention by means of comparing the description in the scope of claims for patent with the description in the detailed description of the invention, and

whether or not a person skilled in the art could solve the problems of the invention by means of referring to the technical common sense upon filing the application even in the absence of the descriptions or the suggestions.

Hereinafter, the invention will be studied based on this viewpoint.

(2) Statement of the scope of claims

The statement of the scope is as described above in item "3".

(3) Description of the detailed description of the invention

The Description of the Patent describes the following matters.

(a) "[0001]

[Field of industrial application] The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, and more particularly, to a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that specifically inhibits the HMG-CoA reductase that is a rate-controlling enzyme in cholesterol biosynthesis, and suppresses the synthesis of cholesterol. Therefore, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor is useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

[0002]

[Conventional Art]

Hypercholesterolemia is a serious risk factor of atherosclerosis, which is a cardiovascular disease that sometimes appears. Thus, studying the influence on activity of HMG-CoA reductase that catalyzes the synthesis of a mevalonic acid based on 3-hydroxy-3-methylglutaryl CoA that plays a main role in the synthesis of cholesterol is necessary for developing new drugs for the treatment of atherosclerosis. As the first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, there are known Mevinolin (U.S. Pat. No. 4,231,938), pravastatin (Japanese unexamined patent application publication No. S59-48418), and simvastatin (U.S. Pat. No. 4,444,784), which are fungal metabolites or chemical modifications. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (F. G. Kathawala et al., 8th Int'l Symp. on Atherosclerosis, Abstract Papers, p. 445, Rome (1988)) and BMY 22089 (GB Pat. No. 2,202,846) have been developed as the second generation drugs."

(b) " [0003]

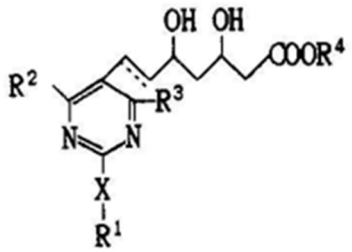
[Problem to be solved by the invention] It is significant in the prevention and the

treatment for atherosclerosis to suppress production of cholesterol as described above, and development of useful drugs is expected from this point of view.

[0004]

[Means for solving problem] Considering the above-described problems and as a result of keen research, the present inventors have discovered that the compound expressed by the following general formula has excellent HMG-CoA reductase-inhibiting activity to complete the present invention. That is, the present invention relates to an HMG-CoA reductase inhibitor comprising a compound expressed by formula (I):

[Chemical formula 9]

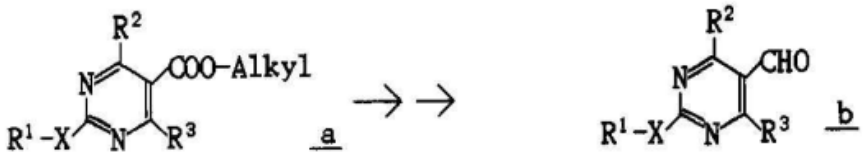


(wherein R^1 is a lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; R^2 and R^3 each is independently hydrogen, a lower alkyl, or aryl, and each of said lower alkyl and aryl may have one or more substituents; R^4 is hydrogen, a lower alkyl, or a cation capable of forming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

(c) "[0010] The compounds of the present invention can be prepared by the following method.

(1) The carboxylate group of the compound a is converted into the alcohol group by the reduction in an appropriate inactive solvent such as THF, ether, or toluene in the presence of the reductant such as $LiA1H_4$ or DIBAL-H. The reaction is performed at -70°C to 50°C, preferably near room temperature, for 10 minutes to 10 hours, preferably for 30 minutes to 3 hours. Then the obtained alcohol is subjected to oxidation in an appropriate solvent such as methylene chloride in the presence of an oxidizing agent such as TPAP/4-methylmorpholin-N-oxide or pyridinium chlorochromate to give aldehyde compound b. The reaction is performed at 0°C to 60°C, preferably near room temperature, for 10 minutes to 10 hours, preferably 30 minutes to 3 hours.

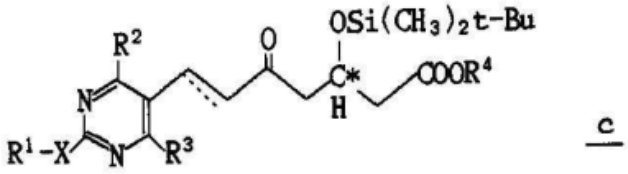
[Chemical formula 10]



(wherein R^1, R^2, and R^3 each has the same meaning as defined above, and Alkyl means lower alkyl.)

[0011] (2) The obtained compound b is subjected to reaction with (3R)-or (3S)-3-(tert-butyldimethylsilyloxy-5-oxo-6-triphenylphosphoranylidene resul acid derivatives in an appropriate organic solvent such as acetonitrile, diethylether, tetrahydrofuran, or dimethylformamide to give the compound c. The reaction is performed for 1 to 30 hours, preferably for 10 to 15 hours, under heating.

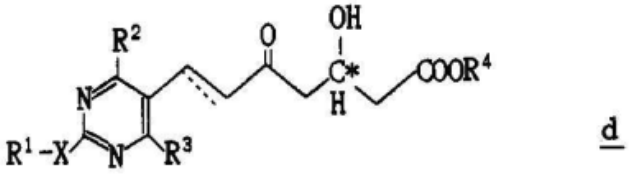
[Chemical formula 11]



(wherein C* means an asymmetric carbon atom, the dotted line means the presence or absence of the double bond, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.)

[0012] (3) The compound c is subjected to reaction to eliminate the tert-butyldimethylsilyl group in an appropriate organic solvent in the presence of hydrogen halogenide to give the compound d. Any type of halogen can be used for hydrogen halogenide. Amongst all, hydrogen fluoride is preferred. The same organic solvents as used in the step (2) may be employed. Acetonitrile is especially preferred. The reaction is performed in a range of 0°C to 60°C, preferably at room temperature, for 0.5 to 10 hours, preferably for 1 to 2 hours.

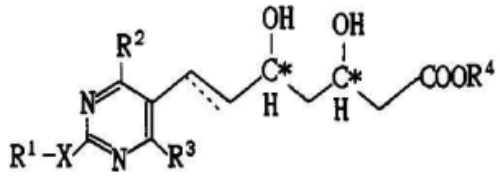
[Chemical formula 12]



(wherein C*, the dotted line, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.

[0013] (4) The compound d is reacted with diethylmethoxyborane and $NaBH_4$ in an alcohol-organic solvent mixture and subjected to column chromatography of silica gel to give the compound (I) (in case R^4 is a lower alkyl). The reaction is performed at a temperature between -100°C to 20°C, preferably between -85°C to -70°C under cooling, for 10 minutes to 5 hours, preferably for 30 minutes to 2 hours. Here, the alcohol used incudes methanol, ethanol, propanol, and butanol; and the organic solvent includes the same as in the step (3). Further, if necessary, the obtained compound may be subjected to saponification in an appropriate alcohol with a solution of metallic hydroxide (R^4: cation), and after the saponification, the reaction mixture can be neutralized with an acid and extracted with an organic solvent (R^4: hydrogen). The saponification can be performed in a popular solvent such as water, alcohol, dioxane, acetone, or a mixture thereof, preferably in the presence of a base, by a conventional method. The reaction is performed at 0°C to 50°C, preferably near room temperature. As metallic hydroxide there may be used sodium hydroxide, potassium hydroxide, or analogues thereof. Acids which may be used include inorganic acids such as hydrochloric acid, sulfuric acid, and the like.

[Chemical formula 13]



(I)

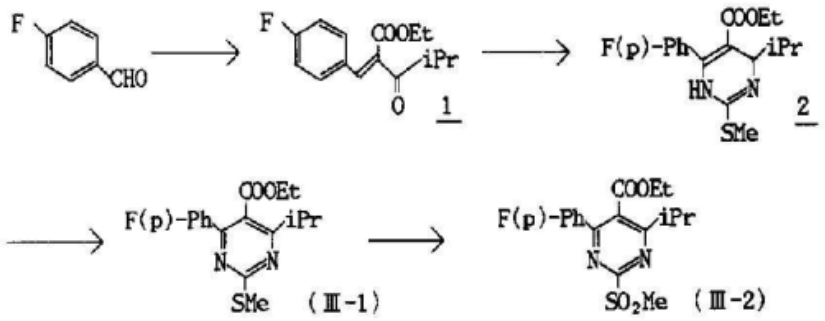
(wherein C*, the dotted line, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.) Further, if necessary, the obtained compounds (I) are subjected to reflux under heating to give the corresponding closed ring lactones of the compounds (I)."

(d) "[0017] [Example]

REFERENCE EXAMPLE 1

Synthesis of Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylthiopyrimidine-5-carboxylate (III-1) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonylpyrimidine-5-carboxylate (III-2)

[Chemical formula 14]



p-Fluorobenzaldehyde 81.81 g was reacted in the same manner as disclosed in the specification of JP Unexamined Pat. Publn. No. 61-40272 to give 1151.0 g (Yield: 86.7%) of the compound 1. Then the mixture of a solution of 144.68 g of the compound 1 in 65 ml of HMPA and 28.24 g of s-methylisourea hydrogen sulfate was stirred at 100°C for 22 hours. Then the reaction mixture was extracted with ether, and washed with saturated sodium hydrogencarbonate and water in order. The organic layer was dried, and the solvent was distilled away. The obtained residue was subjected to column chromatography of silica gel to give 226.61 g (yield: 46.8%) of the compound 2.

[0018]

To a solution of the obtained compound 2 in 400 ml of benzene was added 21.64 g (0.095 mmol) of DDQ, and the mixture was stirred for 30 minutes. Then the mixture was subjected to column chromatography of silica gel to give 24.31 g (Yield: 91.9%) of the compound (III-1).

NMR($CDCl_3$) δ: 1.10 (t, J=7, 3H); 1.31 (d, J=7, 6 Hz); 2.61 (s, 3H); 3.18 (hept, J=7, 1H); 4.18 (q, J=7, 2H); 7.12 (m, 2H); 7.65 (m, 2H)

[0019]

To a solution of 13.28 g (0.04 mmol) of the obtained compound (III-1) in chloroform was added 17.98 g of m-chloroperbenzoic acid, and the reaction mixture was stirred at room temperature. Then it was washed with Na_2SO_3 aqueous solution and saturated sodium hydrogencarbonate in order. The solution was dried, and the solvent was distilled away and washed with n-hexane to give 13.93 g (Yield: 95.7%) of the compound (III-2).

NMR ($CDCl_3$) δ:1.16 (t, J=7, 3H); 1.37 (d, J=7, 6H); 3.26 (hept, J=7, 1H); 3.42 (s, 3H) 4.28 (q, 2H); 7.18 (m, 2H); 7.76 (m, 2H)

The compound (III-2) can be obtained by subjecting the compound 2 to reaction with a permanganic acid potassium salt to oxidize the compound 2 without passing through the compound (III-1) (REFERENCE EXAMPLE 3).

[0020]

REFERENCE EXAMPLE 2

Another synthetic method of the compound (III-1)

To a solution of 200 mg (0.594 mmol) of the compound 2 in 5 ml of dichloromethane were added 0.5 g (6.10 equivalent) of potassium carbonic anhydride and 166 mg (1.1 equivalent) of iodine, and the mixture was stirred at room temperature for 2.5 hours. After reaction, saturated sodium hydrogensulfite was added to the mixture, followed by extraction with ether. The organic layer was washed with water and dried. The solvent was distilled away under reduced pressure to give 166 mg (Yield: 83.6%) of the compound (III-1) as resinous substance.

NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7); 1.31 (d, 6H, J=7); 2.61 (s, 3H); 3.17 (heptet, 1H, J=7); 4.18 (q, 2H, J=7); 7.07-7.17 (m, 2H); 7.61-7.69 (m, 2H)

[0021]

REFERENCE EXAMPLE 3

Another synthetic method of the compound (III-2)

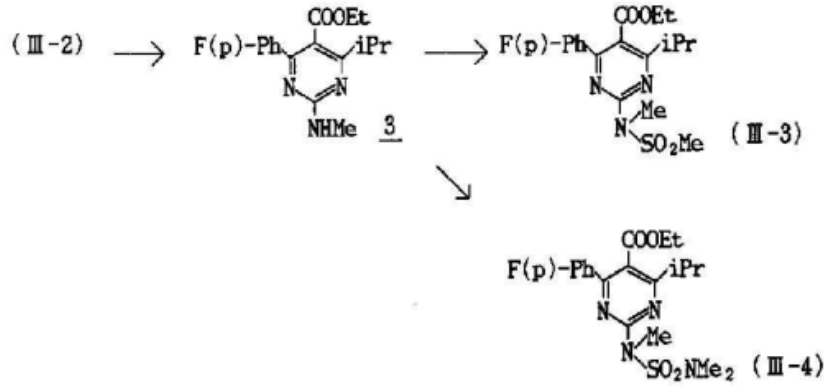
To a solution of 1.0 g (2.97 mmol) of the compound 2 in 10 ml of acetone was added 1.5 g (9.48 mmol) of potassium permanganate, and the mixture was stirred at room temperature for 15 minutes. Acetic acid 1.0 ml was added thereto, and the mixture was stirred at room temperature for another 30 minutes and water was added thereto. The reaction mixture was extracted with ether, washed with saturated sodium hydrogencarbonate and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was distilled away to give 1.07 g (2.94 mmol) (Yield: 99.1%) of the compound (III-2) as crystals.

[0022]

REFERENCE EXAMPLE 4

Synthesis of Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-carboxylate (III-3) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-dimethylsulfamoylamino)pyrimidine-5-carboxylate (III-4)

[Chemical formula 15]



To a solution of 52.7 g (144 mmol) of the compound (III-2) in 500 ml of absolute ethanol, a solution of 71.9 ml of 5N methylamine in ethanol was added gradually under ice-cooling. The reaction mixture was warmed to room temperature, stirred for 1 hour, and evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted with ether, dried, and evaporated under reduced pressure to give 46.9 g (Yield: 100%) of the compound 3.

Mp: 85°C to 86°C

Anal Calcd. (%) for $C_{17}H_{20}N_3FO_2$

Calculated values: C, 64.34; H, 6.35; N, 13.24; F,5.99.

Experimental values: C, 64.42; H, 6.46; N, 13.30; F, 6.14

[0023]

To a solution of 370 mg (1.213 mmol) of the compound 3 in 5 ml of DMF, 60 mg of 60% NaH was added under ice-cooling, and the reaction mixture was stirred for 30 minutes. Methanesulfonyl chloride 208 mg was added thereto, and the mixture was warmed to room temperature and further stirred for 2 hours. Ice-water was added to the mixture, and the mixture was extracted with ether. The organic layer was washed with water and dried. The solvent was evaporated under reduced pressure, and the resulting residue was washed with ether-n-pentane to give 322 mg (Yield: 57.6%) of the compound (III-3).

NMR ($CDCl_3$) δ: 1.10 (t, J=7, 3H); 1.32 (d, J=7, 6H); 3.24 (hept, J=7, 1H); 3.52 (s, 3H); 3.60 (s, 3H); 4.19 (q, J=7, 2H); 7.14 (m, 2H); 7.68 (m, 2H)"

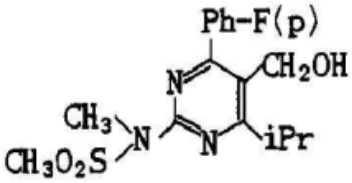
(e) "[0029] EXAMPLE 1

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I a-1)

(1) To a solution of 322 mg of the compound (III-3) obtained in Reference Example 2 in 7 ml of anhydrous toluene, 1.4 ml of DIBAL-H in 1.5M toluene was added dropwise at

-74°C, and the reaction mixture was stirred for 1 hour and acetic acid was added thereto. The mixture was extracted with ether, and the organic layer was washed with sodium bicarbonate and water, dried, and evaporated under reduced pressure to distil ether. The obtained residue was subjected to column chromatography of silica gel eluting with methylene chloride/ether (20/1) to give 277 mg (Yield: 96.1%) of [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl-amino)pyrimid ine-5-yl]methanol 4.

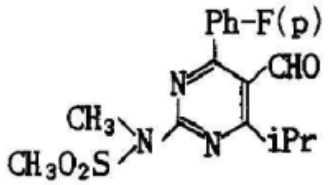
[Chemical formula 17]



4

[0030] (2) A suspension of 277 mg of the thus obtained compound 4, 190 mg of 4-methylmorpholin-N-oxide, 6 mg of TPAP, 1.0 g of powder molecular sieve 4A, and 10 ml of methylene chloride was stirred for 2 hours. The insoluble matter was filtered off and two-thirds of the filtrate was distilled away under reduced pressure. The resulting residue was subjected to column chromatography of silica gel eluting with methylene chloride to give 196 mg (Yield: 71.2%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimi dine-5-carbardehyde 5 as crystals.

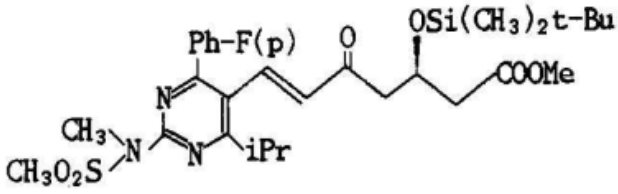
[Chemical formula 18]



5

[0031] (3) A solution of 190 mg of the compound 5, 450 mg of methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate (Reference Example 6), and 5 ml of acetonitrile was refluxed under heating for 14 hours and evaporated under reduced pressure to distill acetonitrile. The resulting residue was subjected to column chromatography of silica gel eluting with methylene chloride to give 233 mg (Yield: 71.3%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimi dine-5-yl]-(3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-(E)-6-heptenate 6 as syrup.

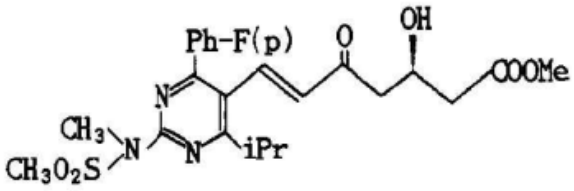
[Chemical formula 19]



6

[0032] (4) To a solution of 16 g of the compound 6 in 100 ml of acetonitrile a solution of 48% hydrogen fluoride in 400 ml of acetonitrile (1:19) was added dropwise under ice-cooling, and the mixture was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was neutralized with sodium bicarbonate and extracted with ether. The organic layer was washed with sodium chloride, dried and evaporated under reduced pressure to distil ether to give 13 g (Yield: 100%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimi
dine-5-yl]-(3R)-3-hydroxy-5-oxo-(E)-6-heptenate 7 as syrup.

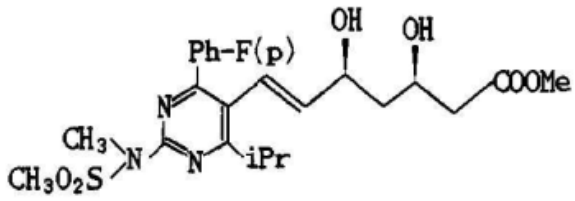
[Chemical formula 20]



7

[0033] (5) To a solution of 13 g of the compound 7 in 350 ml of anhydrous THF and 90 ml of methanol, a solution of 29.7 ml of 1M diethylmethoxyborane-THF was added at -78°C, and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added 1.3 g of $NaBH_4$, and the mixture was stirred for 3 hours. Acetic acid 16 ml was added thereto, and the mixture was adjusted to pH 8 with saturated sodium bicarbonate and extracted with ether. The organic layer was washed with water, dried, and evaporated ether under reduced pressure. To the resulting residue was added methanol, and the mixture was evaporated under reduced pressure three times. The resulting residue was subjected to column chromatography of silica gel eluting with methylene chloride/ether (3/1) to give 11.4 g (Yield: 85.2%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrim
idine-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ib-1) as syrup.

[Chemical formula 21]

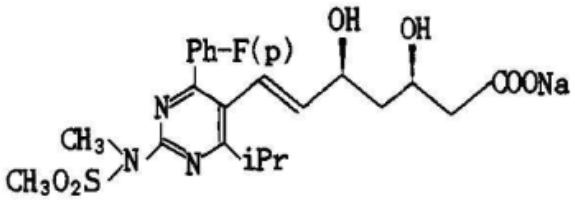


(I b-1)

NMR ($CDCl_3$) δ:1.27 (d, J=7, 6H); 1.53 (m, 2H); 2.47 (d, J=6,2H); 3.36 (hept, J=2 (H); 3.52 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 4.20 (m, 1H); 4.43 (m, 1H); 5.45 (dd, J=5, 16, 1H); 6.64 (dd, J=2, 16, 1H); 7.09 (m, 2H); 7.64 (m, 2H)

[0034] (6) To a solution of 11.4 g of the compound (I b-1) in 160 ml of ethanol, 223 ml of 0.1N sodium hydroxide was added under ice-cooling. The reaction mixture was warmed to room temperature and stirred for 1 hour. The solvent was distilled away under reduced pressure, and ether was added to the resulting residue and the mixture was stirred to give 11.0 g (Yield: 95.0%) of the objective compound (Ia-1) as powdery crystals.

[Chemical formula 22]



(I a-1)

$[\alpha]_D$ =+18.9±0.6°C (C=1.012, 25.0°C, H_2O) NMR ($CDCl_3$) δ: 1.24 (d, J=7, 6H); 1.48 (m, 1H); 1.65 (m, 1H); 2.27 (dd, J=2,6.2H); 3.41 (hept, J=7, 1H); 3.48 (s, 3H); 3.59 (s, 3H); 3.73 (m, 1H); 4.32 (m 1H); 5.49 (dd, J=7, 16, 1H); 6.62 (d, J=16, 1H); 7.19 (m, 2H); 7.56 (m, 2H)"

(f) " [0039] EXAMPLE 8

Method for the synthesis of calcium salt of the compound (I a-1)

The compound (I a-1) (sodium salt) 1.50 g (3.00 mmol) was dissolved in 15 ml of water and stirred at room temperature under nitrogen atmosphere, and successively 3.00 ml (3.00 mmol) of 1 mol/L calcium chloride 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 a powder. This compound started to melt at a temperature of 155°C, but the definitive melting point was ambiguous.

$[\alpha]_D$ =+6.3° ±0.2°C (C=2.011, 25.0°C, MeOH).
Anal Calcd. (%) for $C_{22}H_{27}N_3O_6SF \bullet 0.5Ca \bullet 0.5H_2O$
Calculated values: C, 51.85; H, 5.53; N, 8.25; F, 3.73; Ca, 3.93
Experimental values: C, 51.65; H, 5.51; N, 8.47; F, 3.74; Ca, 4.07"
(g) " [0040] Biological Activity
[Experiment]
HMG-CoA reductase inhibitory action
(1) Preparation of rat liver microsome

Sprague-Dawley rats, which had free access to ordinary diet containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsome. The thus obtained microsome was purified according to the manner described by Kuroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105,000×g was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). It 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 maintained at -80°C.

[0041] (2) Measurement method of the HMG-CoA reductase inhibitory activities

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 (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 maintained at 0°C. The microsome solution (1.675 ml) was mixed with 670 μl of 25 mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to a solution of 670 μl of 0.5 mM [3^{-14}C]HMG-CoA (3mCi/mmol). A solution (5 μl) of sodium salt of the test compound dissolved in potassium phosphate buffer was added to make 45 μl of the mixture. 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 and then 30 μl of this mixture was subjected to thin-layer chromatography of silica gel of 0.5 mm in thickness (Merck AG, Art 5744). The chromatograms were developed in toluene/acetone (1/1) and the spots, whose Rf value was between 0.45 to 0.60, were 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 present compounds are shown in Table 4 as comparative ones based on

the assumption that the inhibitory activity of Mevinolin (sodium salt) measured by the method as a reference drug is 100.

[0042]

[Table 4]

表 4

被検化合物	相対活性
Ｉａ－1	442
Ｉａ－3	385
Ｉａ－5	279
Ｉａ－7	260
メビノリンNa	100

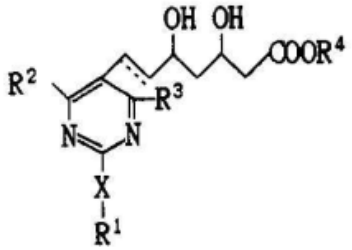
被検化合物　　Test Compound
相対活性　　Relative Activitiy
メビノリンＮａ　　Mevinolin Na

From the test data, the compounds of the present invention are considered to be an effective agent that exhibits HMG-CoA reductase inhibition activities superior to that of Mevinolin."

(4) Problems to be solved of the Invention

The detailed description of the invention of the Description of the Patent describes that "it is significant in the prevention and the treatment for atherosclerosis to suppress production of cholesterol, and development of useful drugs is expected from this point of view", and considering the above-described problems, the present inventors have discovered that the compound expressed by the following general formula (I) has excellent HMG-CoA reductase-inhibiting activity to complete the present invention,

"



(wherein R^1 is a lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; R^2 and R^3 each is independently hydrogen, a lower alkyl, or 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 sulfonyl group, or an imino group which may have a substituent; the dotted line represents the presence or absence of a double bond)" (see summarization b).

Since the compound expressed by the general formula (I) includes compounds of the Inventions 1, 2, 5, 9 to 11, and an HMG-CoA reductase inhibitor comprising the compound of the Invention 1 as an active ingredient defines the Invention 12, the problems to be solved by the Inventions 1, 2, 5, 9 to 11 are to provide a compound having excellent HMG-CoA reductase-inhibiting activity, while the problem to be solved by the Invention 12 is to provide an HMG-CoA reductase inhibitor including the compound.

While the detailed description of the invention describes that the Invention relates to "3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor", and that mevinolin, pravastatin, and simvastatin, which are fungal metabolites or of the chemical modifications, and synthetic inhibitors of HMG-CoA reductase such as fluvastatin and BMY 22089 were developed as the above-described HMG-CoA reductase inhibitors (see summarization a), there is no description as to whether these already developed HMG-CoA reductase inhibitors have problems to be solved. Thus, the Invention is acknowledged to have a problem to be solved that is to provide a compound "having excellent HMG-CoA reductase-inhibiting activity" to the extent possible to become a drug that "suppresses production of cholesterol", or an HMG-CoA reductase inhibitor comprising the compound as an active ingredient, but not a compound that needs excellent HMG-CoA reductase-inhibiting activity greater than those of mevinolin, pravastatin, simvastatin, and fluvastatin that were already developed HMG-CoA reductase inhibitors.

(5) Comparison / Judgment

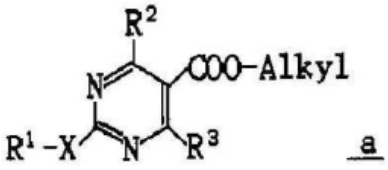
Since the problem to be solved by the Invention is to provide a compound having excellent HMG-CoA reductase-inhibiting activity, or an HMG-CoA reductase inhibitor including the compound, whether the compounds of the Inventions 1, 2, 5, 9 to 11 can be obtained (can be produced) and whether the obtained compounds have excellent HMG-CoA reductase-inhibiting activity are described in the detailed description of the invention so that a person skilled in the art can understand will be examined as follows.

A Production

The detailed description of the invention describes a "calcium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino pyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" that is included in the Invention 1, and describes, as Examples 1 and 2, a specific production method for producing "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin) -5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid sodium salt" from a starting ingredient (III-3) to form a "(hemi)calcium salt" (see summarizations e and f). In addition, the detailed description of the invention describes, as Reference Examples 1 to 4, a specific production method for producing a compound that is the starting ingredient (III-3) (see summarization d).

While the "calcium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino pyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid" that is specifically described as an Example corresponds with a case in the formula (I) indicated in the Invention 1, wherein R^1 is methyl, R^2 represents phenyl substituted by fluorine, R^3 represents isopropyl, R^4 represents calcium ion, X represents an imino group substituted by a methylsulfonyl group, and the dotted line represents the presence of a double bond, there is a general description about the production method of the formula (I) in the detailed description of the invention, and there is also a description about the production method in which R^4 represents H in the Invention 1 (see summarization c). In addition, in the above-described general description, there is a description that the following compound a,

"



a

" is produced as a starting ingredient (see summarization c). The compound a corresponds to the above-described compound (III-3); however, it can be said that a person skilled in the art can understand that taking into consideration Reference Examples 1 to 4, which are the production examples thereof (see summarization d), changing a part of the test reagents described therein can produce a compound in the formula (I), wherein R^1 is not only methyl but also the other lower alkyl, R^2 represents phenyl substituted by not only fluorine but also the other halogens, R^3 represents not only isopropyl but also the other lower alkyl, and X represents an imino group substituted by not only a methylsulfonyl group but also the other alkylsulfonyl groups.

Thus, it can be said that a person skilled in the art can understand that the compound of the Invention 1 can be actually produced; that is, provided, based on the description of the detailed description of the invention.

As described above in (3) (3-2), (3-3), (3-4), the Inventions 2, 5, and 9 are compounds of the Invention 1, which are partly limited in the formula (I). Thus, it can be said that a person skilled in the art can understand that the compounds of the Inventions 2, 5, and 9 can be also produced if the compounds can be produced within the range indicated in the formula (I) of the Invention 1.

While the Invention 10 is produced in a specific production method, a general production method thereof is described in the detailed description of the invention as described above (see summarization c), and a specific example thereof is also described therein (see summarizations e and f), so that it can be said that a person skilled in the art can understand that the compound of the Invention 10 can be also produced.

In addition, the Invention 11 is actually produced in the above-described Examples 1 and 2 (see summarizations e and f).

Thus, it can be said that the production of the Invention 11 is described in the detailed description of the invention to the extent that a person skilled in the art can understand that the compounds of the Inventions 1, 2, 5, and 9 to 11 can be produced.

B HMG-CoA reductase-inhibiting activity

The detailed description of the invention describes, as a measurement method of the HMG-CoA reductase inhibitory activities, about mixing a mixture of a rat liver

microsome solution and a [3-^{14}C]HMG-CoA solution with a test compound to incubate to develop the resulting mixture on thin-layer chromatography plates to scrape the chromatograms whose Rf value was between 0.45 to 0.60 to measure the specific radio-activities of the obtained products based on the assumption that the relative activity of a mevinolin sodium salt as reference drug is 100 (see summarization g), and describes that as a result of the measurement, the compound (Ia-1) that is a "sodium salt" of "(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid has HMG-CoA reductase inhibitory action of 442 relative activity based on the assumption that the relative activity of a mevinolin Na as reference drug is 100 (see summarization g).

The compound (Ia-1) described in the detailed description of the invention is a sodium salt, which is not included in the Invention 1 which is a free acid or a hemicalcium salt, but is understood to have the same pharmaceutical benefit as the Invention 1 irrespective of the salt form in view of the pharmacological action mechanism as described above in 1 (3) (3-1) C. Thus, the invention 1 can be assumed to also indicate HMG-CoA reductase-inhibiting activity similar to that of a sodium salt. In fact, according to Evidence A No. 3, the hemicalcium salt "S-4522" indicates HMG-CoA reductase-inhibiting activity stronger than that of a mevinolin sodium salt (see summarizations 3a an 3b) , which supports the above-described assumption.

The Invention 1 includes a compound expressed by formula (I) where R^1 represents low-grade alkyl, R^2 represents phenyl replaced with a halogen, R^3 represents a low-grade alkyl, and X represents an imino group replaced with an alkylsulfonyl group, within its range, in which the substituent groups are very similar to the imino group in the Example where R^1 is methyl, R^2 represents phenyl substituted by fluorine, R^3 represents isopropyl, and X represents an imino group substituted by a methylsulfonyl group. Since the compound (Ia-1) indicates stronger activity than mevinolin Na that is a drug, a person skilled in the art can understand that the Invention 1 that has a very similar chemical constitution to the compound (Ia-1) also becomes a compound indicating similar HMG-CoA reductase-inhibiting activity, and thus the Invention 1 can be said to have "excellent HMG-CoA reductase-inhibiting activity" to the extent possible to become a drug that "suppresses production of cholesterol".

Thus, it can be said that the detailed description of the invention describes to the extent that a person skilled in the art can understand that the Invention 1 can solve the problem.

In addition, since the Inventions 1, 2, 5, and 9 to 11 are included in the

Invention 1, it can be said that the detailed description of the invention describes to the extent that a person skilled in the art can understand that the Inventions 1, 2, 5, and 9 to 11 can solve the problems.

Further, since the Invention 12 is an HMG-CoA reductase inhibitor including the Invention 1 as an active ingredient, it can be said that the detailed description of the invention describes to the extent that a person skilled in the art can understand that the Invention 12 can solve the problem.

(6) Allegation of the demandant

A Outline of the allegation of the demandant (the written statement dated on March 24, 2016, p. 23, l. 14 to p. 29, l. 20, the oral proceedings statement brief, p. 15, l. 6 to p. 16, l. 8)

The problem to be solved by the Invention is "to provide an HMG-CoA reductase inhibitor including a compound having excellent HMG-CoA reductase-inhibiting activity", and "being excellent" therein means "being excellent" to an extent greater than the prior art.

While the closest prior art to the Invention is the A 1 Invention, there is no description about comparative data between the Invention and A 1 Invention in the detailed description of the invention in the Description of the Patent. Thus, it cannot be said that the problem can be solved based on only the detailed description of the invention.

While the detailed description of the invention in the Description of the Patent describes about the relative activity of the compound of the Invention compared with mevinolin Na in a case where the compound is a sodium salt in the measurement test of HMG-CoA reductase-inhibiting activity using a microsomal fraction, there is no description of indexes that indicate the measurement numbers and variations, so that the measurement results can be understood to have been obtained by only one-time measurement, and it is unknown whether the inhibiting activity means an IC_{50} value, the largest activity, or an inhibitory rate of a specific concentration. The measurement test of HMG-CoA reductase-inhibiting activity using a microsomal fraction belongs to the test systems that produce results that vary widely, where not only IC_{50} values vary but also the strength/weakness of the activity could reverse also in the same test (Evidences A Nos.7, 8, and 31), so that it cannot be understood that the Invention has HMG-CoA reductase-inhibiting activity more excellent even than that of mevinolin.

Meanwhile, seeing the IC_{50} value of HMG-CoA reductase-inhibiting activity of the compound of the A 1 Invention (see summarization 1c) and the IC_{50} value of

HMG-CoA reductase-inhibiting activity of the mevinolin Na disclosed in Evidence A No. 8, the compound of A 1 Invention can be understood to have HMG-CoA reductase-inhibiting activity that is 2.6 times stronger than that of mevinolin Na; however, according to Table 4 in the Description of the Patent, the compound of the Invention has HMG-CoA reductase-inhibiting activity that is 4.42 times stronger than that of mevinolin Na while having HMG-CoA reductase-inhibiting activity that is 2 times stronger than that of mevinolin Na in the experiment disclosed in Evidence A No. 3. Thus, it cannot be recognized with certainty that the compound of the Invention has more excellent inhibiting activity than the A 1 Invention.

Next, since the detailed description of the invention describes, as the prior art, that the second generation synthetic HMG-CoA reductase inhibitors such as fluvastatin and BMY 22089 were developed against the first generation HMG-CoA reductase inhibitor such as mevinolin, pravastatin, and simvastatin, the compound of the Invention needs to have more "excellent HMG-CoA reductase-inhibiting activity" than the second generation HMG-CoA reductase inhibitors, not than the first generation mevinolin Na.

Evidence A No. 8 discloses that fluvastatin has activity that is 10 times stronger than that of mevinolin Na. Evidence A No. 19 discloses that fluvastatin has activity that is 3.4 times stronger than that of mevinolin Na. Evidences A No. 15 and 19 disclose that (+) BMY21950 (an activated form of BMY22089) has activity that is 1.4 times stronger than that of lovastatin (mevinolin Na). Meanwhile, the detailed description of the invention describes that the compound of the Invention has activity that is 4.4 times stronger than that of mevinolin Na as described above.

While the Description of the Patent describes that the compound of the Invention has HMG-CoA reductase-inhibiting activity that is 4.4 times stronger than that of mevinolin Na as described above, the data have been obtained by only one-time measurement test that produces results that vary widely, and a person skilled in the art cannot recognize from the test result that the compound of the Invention has HMG-CoA reductase-inhibiting activity more excellent than those of fluvastatin and (+) BMY21950 (an activated form of BMY22089).

B Examination on the allegation of the demandant

While the detailed description of the invention describes, as the prior art, that the second generation synthetic HMG-CoA reductase inhibitors such as fluvastatin and BMY 22089 in addition to the first generation drugs of mevinolin, pravastatin, and simvastatin, which are fungal metabolites or chemical modifications, were developed (see summarization a), it is natural to understand that the description means that the

second generation HMG-CoA reductase inhibitors that define synthetic compounds were developed against the first generation HMG-CoA reductase inhibitors, which are so-called natural compounds that are fungal metabolites or chemical modifications. Considering that there is no description that the first generation HMG-CoA reductase inhibitors and the second generation HMG-CoA reductase inhibitors have some problems such as having low HMG-CoA reductase-inhibiting activity as described above in the item (4), the compound of the Invention is acknowledged to have a problem to be solved that is to provide a compound that has "excellent HMG-CoA reductase-inhibiting activity" to the extent possible to become a drug that "suppresses production of cholesterol", but not a compound that needs HMG-CoA reductase-inhibiting activity greater than those of mevinolin, pravastatin, simvastatin, and fluvastatin that were already developed HMG-CoA reductase inhibitors.

Thus, the allegation of the demandant that is based on the assumption that the Invention has a problem to be solved that is to provide a compound that has excellent HMG-CoA reductase-inhibiting activity greater than those of A 1 Invention and the second generation HMG-CoA reductase inhibitors cannot be accepted from the beginning.

In addition, as Evidences A Nos. 7 and 8 use test methods using a rat liver microsome as described in 1 (3) (3-1) C, it can be understood that even if producing results that vary widely, the measurement method of HMG-CoA reductase-inhibiting activity described in the Description of the Patent at the time of filing of the present application was a general method for measuring the activity (see Evidence B No. 31). Seeing Table 4 of the Description of the Patent indicating the HMG-CoA reductase-inhibiting activity of the sodium salt and the HMG-CoA reductase-inhibiting activity of the mevinolin Na, which is not the Invention 1 itself, based on the above-described acknowledgement, even if there is no description of indexes of the relative activities (whether the indexes are IC_{50} values) or no description as to what data are used to calculate the measurement results (the measurement numbers and variations) in Table 4 in the description of the Invention, lack of description thereof does not mean that the results of Table 4 are immediately untrustworthy. Because it can be understood that the sodium salt and the mevinolin Na were at least measured under the same conditions, and the results showing that the compound of the Invention 1 in a case where the compound is a sodium salt has higher activity than that of mevinolin Na are obtained, it cannot be said that the results are untrustworthy so long as no evidence that specifically denies the results is indicated.

As described above in (5) B, even if a free acid or a hemicalcium salt is used

instead of a sodium salt, the compound can be assumed to also indicate HMG-CoA reductase-inhibiting activity similar to that of a sodium salt. In fact, according to Evidence A No. 3, the hemicalcium salt "S-4522" indicates HMG-CoA reductase-inhibiting activity stronger than that of a mevinolin sodium salt (see summarizations 3a an 3b) , which supports the above-described assumption.

Therefore, the allegation of the demandant cannot be accepted.

(7) Summary

As described above, the invention for which a patent is sought described in the Inventions 1, 2, 5, and 9 to 12 cannot be said to not be described in the detailed description of the invention. Therefore, it cannot be said that the description of the scope of claims for the Patent does not comply with Article 36(5)(i) of the Patent Act before revision by the Act No. 116 of 1994.

No. 8 Closing remarks

As described above, it cannot be said that the patent for the Inventions 1, 2, 5, and 9 to 12 violates the provisions of Article 29 of the Patent Act, falls under Article 123(1) (ii), and should be invalidated.

In addition, it cannot be said that the description of the scope of claims for the patent for the Inventions 1, 2, 5, and 9 does not comply with Article 36(5)(i) of the Patent Act before revision by the Act No. 116 of 1994, so that it cannot be said the patent for the Inventions 1 to 5, and 7 to 12 is granted for a patent application that does not meet the requirement stipulated in Article 36(5) of the Patent Act, and falls under Article 123(1)(iv) and should be invalidated.

Therefore, the patent for the Inventions 1, 2, 5, and 9 to 12 cannot be invalidated by the reasons and evidences that the demandant alleged.

The costs in connection with the trial shall be borne by the demandant under the provisions of Article 61 of the Code of Civil Procedure which is applied mutatis mutandis in the provisions of Article 169(2) of the Patent Act.

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

July 5, 2016

Chief administrative judge: INOUE, Masahiro

Administrative judge: NAKATA, Toshiko

Administrative judge: SERA, Satoki