Patent Right	Date	June 17, 2020	Court	Intellectual Property High Court, Second Division
	Case number	2019 (Gyo-Ke) 10118		
- A case in which, in a lawsuit for a rescission of a JPO decision with regard to an invention titled "TOPICAL OPHTHALMIC FORMULATIONS CONTAINING DOXEPIN DERIVATIVES FOR TREATING ALLERGIC EYE DISEASES", in a court to which the case was remanded, an invention step was acknowledged, based on the determination that it can be acknowledged that an effect of the invention is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention.				

Case type: Rescission of Trial Decision to Maintain

Result: Dismissed

References: Article 29, paragraph (2) of the Patent Act

Related rights, etc.: Patent No. 3068858

Decision of JPO: Invalidation Trial No. 2011-800018 (trial decision rendered on December 1, 2016)

Summary of the Judgment

1. Outline of Procedures at the JPO and History of Lawsuit, etc.

(1) Previous Lawsuit Judgment

On January 22, 2013, the JPO rendered a trial decision to maintain the patent of the present case (hereinafter referred to as "the Second Trial Decision"), regarding Invalidation Trial No. 2011-800018 case filed by the Plaintiff, based on the determination that it cannot be deemed that the invention of the present case would have been motivated from the invention disclosed in Exhibit Ko 1 (hereinafter referred to as "Invention of Exhibit Ko 1") and the invention disclosed in Exhibit Ko 4 (hereinafter referred to as "Invention of Exhibit Ko 4"). However, on July 30, 2014, the Intellectual Property High Court rendered a judgment to rescind the Second Trial Decision (hereinafter referred to as "the Previous Lawsuit Judgment"). Thereafter, the Previous Lawsuit Judgment became final and binding.

(2) Decision and Judgment, etc., after the Previous Lawsuit Judgment

On December 1, 2016, the JPO rendered a trial decision to accept the request for a correction filed on February 1, 2016 (hereinafter referred to as "the Present Correction", the invention according to Claim 1 after the correction is referred to as "Present Invention 1", the invention according to Claim 5 after the correction is referred to as "Present Invention 2", and these inventions are collectively referred to as "the Present Inventions") and to maintain the patent of the present case. However,

on November 21, 2017, the Intellectual Property High Court rendered a judgment to rescind the trial decision of the present case (hereinafter referred to as the "the Judgment before the Remand"). The Judgment before the Remand held that on the premise that the configuration of each of the Present Inventions would have been easily conceivable from the Invention of Exhibit Ko 1 and the Invention of Exhibit Ko 4 to a person ordinarily skilled in the art, it cannot be deemed that an effect of each of the Present Inventions is a remarkable effect which would have been difficult to predict by a person ordinarily skilled in the art, and thus, held that the trial decision of the present case erred in the determination concerning the effect of each of the Present Inventions.

The final appellate court quashed the Judgment before the Remand, and remanded the present case to the Intellectual Property High Court on the grounds that the Judgment before the Remand was unlawful in interpreting and applying the laws and regulations, because the Judgment before the Remand rescinded the trial decision of the present case due to the fact that the Judgment before the Remand denied that the effect of each of the Present Inventions is remarkable and unpredictable.

2. Reason 1 for Rescission (Reason 2 for Invalidation: Erroneous Determinations of Inventive Step Based on Invention of Exhibit Ko 1)

(1) The Previous Lawsuit Judgment determined that with regard to each of the Present Inventions, there would have been a motivation to arrive at the configuration of the invention. In this regard, even when there would have been a motivation to arrive at the configuration of the invention, in the case where an effect of the invention is remarkable to the extent that the effect of the invention exceeds the effect that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention at the time of the priority date, it cannot be acknowledged that such invention could have been easily made by a person ordinarily skilled in the art. The Previous Lawsuit Judgment did not determine to the extent whether or not each of the Present Inventions has such an unpredictable and remarkable effect, and therefore, it is construed that the binding effect of the Previous Lawsuit Judgment (Article 33, paragraph (1) of the Administrative Case Litigation Act) does not extend to this issue.

(2) Present Invention 1

A. According to the description of the present case, in an experiment to measure an inhibition rate of histamine release from human conjunctival mast cells by administering a drug to a cell population in which human conjunctival mast cells were cultured, with regard to the compound of the Present Invention (hereinafter referred to

as "the present compound"), it can be acknowledged that an inhibition rate of histamine release from human conjunctival mast cells increased in a concentration-dependent manner between 30 μM and 2000 μM, to a maximum value of 92.6%, and between these concentrations, unlike the cases of cromolyn sodium and nedocromil sodium, a phenomenon of decreasing the inhibition rate did not occur with higher doses (concentrations) than the dose (concentration) at which the maximum inhibition rate was reached.

B(A) With regard to the present compound, there is no evidence that it can be acknowledged that the above A was clear at the time of the priority date of the present case.

(B) It can be acknowledged that ketotifen has an application as a human conjunctival mast cell stabilizing agent in humans, in contrast to the results of experiments in guinea pigs (Exhibit Ko 1), where the inhibition rate of histamine release was 67.5% at 5 minutes after the induction and 67.2% at 10 minutes after the induction. However, there is no evidence that it can be acknowledged that, at the time of the priority date of the present case, it was clear whether or not ketotifen has a concentration-dependent effect on an inhibition rate of histamine release from human conjunctival mast cells between 30 μM and 2000 μM.

In addition, there is no evidence that it can be acknowledged that it was known to a person ordinarily skilled in the art at the time of the priority date of the present case that Chlorpheniramine (chlorpheniramine), which is stated in Exhibit Ko 1 as not having an inhibitory effect on histamine release in the conjunctiva in guinea pigs as well as Ketotifen (ketotifen) and the present compound, has a stabilizing effect on human conjunctival mast cells.

Further, anti-allergic drugs with a tricyclic skeleton include amelexanox (Amelexanox in Exhibit Ko 1) and nedocromil sodium as well as the present compound and ketotifen. However, only the fact that the compounds are common to the extent that they are tricyclic compounds does not provide a basis for a person ordinarily skilled in the art to expect the same kind and the same level of efficacy in stabilizing human conjunctival mast cells.

Therefore, it cannot be deemed that a person ordinarily skilled in the art, who had read the disclosure of Exhibit Ko 1, could have predicted from the effect of ketotifen that the present compound would have the effect on human conjunctival mast cells as mentioned in the above A.

(C) At the time of the priority date of the present case, even if there were documents on inhibitory effects of eye drop solutions containing procaterol

hydrochloride, disodium cromoglycate, and pemirolast potassium on the reaction to patients with cedar pollen allergy (Exhibits Ko 20, 34, and 37), the chemical structure of the present compound is remarkably different from those of procaterol hydrochloride (Exhibit Ko 20), disodium cromoglycate (Exhibit Ko 34), and pemirolast potassium (Exhibit Ko 37). In addition, from the experimental results as disclosed in Exhibits Ko 20, 34, and 37, it cannot be acknowledged that it is clear whether or not procaterol hydrochloride (Exhibit Ko 20), disodium cromoglycate (Exhibit Ko 34), and pemirolast potassium (Exhibit Ko 37) have concentration-dependent effects between 30 μM and 2000 μM on the inhibition rate of histamine release from human conjunctival mast cells.

Therefore, from each disclosure of Exhibits Ko 20, 34, and 37, it cannot be deemed that it would have been possible to predict that the present compound would have the effect on inhibiting histamine release from human conjunctival mast cells as mentioned in the above A.

C. According to the above, it can be acknowledged that the effect of Present Invention 1 is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention. Therefore, it cannot be acknowledged that Present Invention 1 could have been easily made by a person ordinarily skilled in the art.

(3) Present Invention 2

Present Invention 2 is limited to the Z form (cis isomer) of the present compound of Present Invention 1. Further, in Present Invention 2, the matter "inhibits histamine release from a human conjunctival mast cell by 66.7% or more" for defining the invention is added to Present Invention 1. Then, Present Invention 2 achieves the same effect as Present Invention 1. According to the above (2), it can be deemed that the effect of Present Invention 2 is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted from Exhibits Ko 1 and 4, and the common general technical knowledge at the time of the priority date of the present case.

Further, it cannot be acknowledged that a person ordinarily skilled in the art could have predicted the effects of the present compound on the basis of the effect of ketotifen and Exhibits Ko 20, 34, and 37, as mentioned in the above (2).

Therefore, it cannot be acknowledged that Present Invention 2 could have been easily made by a person ordinarily skilled in the art.

Judgment rendered on June 17, 2020
2019 (Gyo-Ke) 10118 A case of seeking rescission of the JPO decision
Date of conclusion of oral argument: February 17, 2020

Judgment

Plaintiff: X

Defendant: Alcon Research, Ltd.

Former Trade Name: Kyowa Hakko Kirin Co., Ltd.
Defendant: Kyowa Kirin Co., Ltd.

Main Text

1. The Plaintiff's claim shall be dismissed.
2. The court costs shall be borne by the Plaintiff.

Facts and Reasons

No. 1 Claim

A trial decision for Invalidation Trial No. 2011-800018 rendered by the JPO on December 1, 2016 shall be rescinded.

No. 2 Outline of the Case

The present case is a lawsuit seeking rescission of the JPO decision to maintain with regard to a request for a trial for patent invalidation. The issue is whether or not the inventions of Claims 1 and 5 after the correction of the patent of the present case have an inventive step (a remarkable effect).

1. Outline of Procedures at the JPO and History of Lawsuit, etc.

(1) The Defendants are patentees of a patent right for an invention titled "TOPICAL OPHTHALMIC FORMULATIONS CONTAINING DOXEPIN DERIVATIVES FOR TREATING ALLERGIC EYE DISEASES" (Patent No. 3068858, hereinafter referred to as "the present patent right", the patent concerning the present patent right is referred to as "the present patent", Exhibit Ko 81).

The patent application for the present patent was filed on May 3, 1996, claiming priority based on a patent application filed in the United States of America

on June 6, 1995 (this filing date, which forms the basis for the priority claimed, is hereinafter referred to as "the priority date of the present case"). The establishment of the present patent was registered on May 19, 2000 (Exhibit Ko 81).

(2) First Trial Decision

A. On February 3, 2011, the Plaintiff filed a request for a trial for invalidation of the present patent with the JPO, and this case became pending as Invalidation Trial No. 2011-800018.

B. On May 23, 2011, the Defendants filed a request for a correction of the Scope of Claims of the present patent (hereinafter also referred to as "the First Correction").

C. On December 16, 2011, the JPO rendered a trial decision (hereinafter referred to as "the First Trial Decision") to accept the First Correction and to invalidate the patent concerning the inventions of Claims 1 to 12 (Exhibit Ko 82).

D. On April 24, 2012, the Defendants instituted a lawsuit for seeking of a rescission of the First Trial Decision (The Intellectual Property High Court, 2012 (Gyo-Ke) 10145). Thereafter, on June 29, 2012, the Defendants filed a request for a correction trial for correcting the Scope of Claims of the present patent.

E. On July 11, 2012, the Intellectual Property High Court rendered a ruling to rescind the First Trial Decision on the basis of Article 181, paragraph (2) of the Patent Act prior to the revision made by Act No. 63 of 2011.

(3) Second Trial Decision

A. The JPO resumed the proceedings of Invalidation Trial No. 2011-800018 in response to the ruling mentioned in the above (2)E. On August 10, 2012, the Defendants filed a request for a correction of the Scope of Claims of the present patent (hereinafter also referred to as "the Second Correction").

B. The Scope of Claims after the Second Correction is stated as follows (Exhibit Ko 83).

[Claim 1] A human conjunctival mast cell stabilizing agent for ophthalmic use, which is topically administrable and is prepared as an eye drop for the treatment of allergic eye diseases in humans, comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.

[Claim 2] A topically administrable composition for ophthalmic use, which is for the treatment of allergic eye diseases in humans, comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof, wherein the 11-(3-

dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, and is substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, and wherein the topically administrable composition achieves a human conjunctival mast cell stabilizing effect.
(Hereinafter, "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" may be referred to as "the present compound").

C. On January 22, 2013, the JPO rendered a trial decision to accept the Second Correction and to maintain the present patent (hereinafter referred to as "the Second Trial Decision"), based on the determination as follows: it cannot be deemed that the matter "human conjunctival mast cell stabilizing" for defining the invention in each of the inventions after the Second Correction would have been motivated from the invention disclosed in Exhibit Ko 1 (KAMEI Chiaki et al. "Morumotto no Jikken teki Arerugi sei Ketsumakuen ni taisuru Ko Arerugi Yaku no Eikyo (Effects of Antiallergic Drugs on Experimental Allergic Conjunctivitis in Guinea Pigs)" Atarasii Ganka (New Ophthalmology), Vol. 11, No. 4, Pages 603-605, 1994 (in Japanese)) (hereinafter referred to as "Invention of Exhibit Ko 1") and the invention disclosed in Exhibit Ko 4 (Unexamined Patent Application Publication No. 1988-10784) (hereinafter referred to as "Invention of Exhibit Ko 4"); and thus, Reason for Invalidation asserted by the Plaintiff; i.e., lack of an inventive step based on the Invention of Exhibit Ko 1 as the primary cited document, is unfounded (Exhibit Ko 83).

D. On March 1, 2013, the Plaintiff instituted a lawsuit seeking a rescission of the Second Trial Decision (The Intellectual Property High Court, 2013 (Gyo-Ke) 10058).

E. On July 30, 2014, the Intellectual Property High Court rendered a judgment (hereinafter referred to as "the Previous Lawsuit Judgment") to rescind the Second Trial Decision. The Previous Lawsuit Judgment held that the Second Trial Decision erred in determining that "it cannot be deemed that the matter 'human conjunctival mast cell stabilizing' for defining the invention in each of the inventions after the Second Correction would have been motivated from the Invention of Exhibit Ko 1 and the Invention of Exhibit Ko 4, and thus, the Reason for Invalidation asserted by the Plaintiff; i.e., lack of an inventive step based on Invention of Exhibit Ko 1 as the primary cited document, is unfounded", because it can be acknowledged that a person ordinarily skilled in the art, who had read Exhibits Ko 1 and 4, would have been motivated to apply an eyedrop containing KW-4679 (hydrochloride of the cis

isomer of the present compound) for inhibiting allergic conjunctivitis as disclosed in Exhibit Ko 1 to an eye drop for allergic eye diseases in humans, and that when attempting to apply KW-4679, the person ordinarily skilled in the art would have confirmed that KW-4679 has an effect of inhibiting histamine release from human conjunctival mast cells (human conjunctival mast cell stabilizing effect), and would have easily conceived of an idea of applying it to a human conjunctival mast cell stabilizing agent (Exhibit Ko 84). The above judgment became final and binding on January 12, 2016.

(4) Decision after the Previous Lawsuit Judgment

A. The JPO resumed the proceedings of Invalidation Trial No. 2011-800018 in response to the Previous Lawsuit Judgment. On February 1, 2016, the Defendants filed a request for a correction (hereinafter referred to as "the Present Correction", Claims 1 and 5 after the correction are as mentioned in 2 below, the invention according to Claim 1 after the correction is referred to as "Present Invention 1" the invention according to Claim 5 after the correction is referred to as "Present Invention 2", these inventions are collectively referred to as "the Present Inventions", and the description and the drawings after the correction are referred to as "the present description") (Exhibit Ko 207).

B. On December 1, 2016, the JPO rendered a trial decision to accept the Present Correction and to maintain the present patent (the summary of reasons therefor is as mentioned in 4 below, hereinafter referred to as "the Present Trial Decision"). On December 9, 2016, a certified copy of the Present Trial Decision was served on the Plaintiff.

C. On January 6, 2017, the Plaintiff instituted a lawsuit for seeking a rescission of the Present Trial Decision.

(5) Judgment of the Intellectual Property High Court before the Remand

A. On November 21, 2017, the Intellectual Property High Court rendered a judgment to rescind the Present Trial Decision (hereinafter referred to as the "the Judgment before the Remand"). The Judgment before the Remand held that on the premise that the configuration of each of the Present Inventions would have been easily conceivable from the Invention of Exhibit Ko 1 and the Invention of Exhibit Ko 4 to a person ordinarily skilled in the art, it cannot be deemed that an effect of each of the Present Inventions is a remarkable effect which would have been difficult to predict by a person ordinarily skilled in the art, and thus, held that the Present Trial Decision erred in the determination concerning the effect of each of the Present Inventions.

B. The Defendants filed a petition for acceptance of the final appeal against the Judgment before the Remand.

(6) Determination by the Final Appellate Court

The final appellate court quashed the Judgment before the Remand, and remanded the present case to the Intellectual Property High Court on the grounds that the Judgment before the Remand was unlawful in interpreting and applying the laws and regulations, because the Judgment before the Remand rescinded the Present Trial Decision due to the fact that the Judgment before the Remand denied that the effect of each of the Present Inventions is remarkable and unpredictable.

2. Statement of the Scope of Claims

After the Present Correction, the statement of Claims 1 and 5 in the Scope of Claims of the present patent is as follows.

[Claim 1] A human conjunctival mast cell stabilizing agent for ophthalmic use, which is topically administrable and is prepared as an eye drop for the treatment of allergic eye diseases in humans, comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof (the same as Claim 1 before the Present Correction).

[Claim 5] A human conjunctival mast cell stabilizing agent for ophthalmic use, which is topically administrable and is prepared as an eye drop for the treatment of allergic eye diseases in humans, comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof, wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, and is substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, and wherein the human conjunctival mast cell stabilizing agent inhibits histamine release from a human conjunctival mast cell by 66.7% or more.

3. Reasons for Invalidation Asserted by the Plaintiff

(1) Reason 1 for Invalidation (Lack of Novelty Based on Exhibit Ko 1 as Primary Cited Document)

Each of the Present Inventions is the Invention of Exhibit Ko 1, which is a publication distributed prior to the priority date of the present case.

(2) Reason 2 for Invalidation (Lack of Inventive Step Based on Exhibit Ko 1 as Primary Cited Document)

Each of the Present Inventions could have been easily made by a person ordinarily skilled in the art on the basis of the Invention of Exhibit Ko 1 and the Invention of Exhibit Ko 4.

(3) Reason 3 for Invalidation (Lack of Inventive Step Based on Exhibit Ko 3 as Primary Cited Document)

Each of the Present Inventions could have been easily made by a person ordinarily skilled in the art on the basis of the invention disclosed in Exhibit Ko 3 (Unexamined Patent Application Publication No. 1987-45557) (hereinafter referred to as "Invention of Exhibit Ko 3") as well as the Invention of Exhibit Ko 1 and the Invention of Exhibit Ko 4.

4. Summary of Reasons of the Present Trial Decision

(1) Reason 1 for Invalidation (Lack of Novelty Based on Exhibit Ko 1 as Primary Cited Document)

It cannot be deemed that each of the Present Inventions is the Invention of Exhibit Ko 1. Thus, Reason 1 for Invalidation is unfounded.

(2) Reason 2 for Invalidation (Lack of Inventive Step Based on Exhibit Ko 1 as Primary Cited Document)

A. Present Invention 1

(a) The Plaintiff asserts the following different features between Present Invention 1 and the Invention of Exhibit Ko 1.

a. Different Feature 1

With regard to allergic eye diseases, Present Invention 1 is specified as "in humans". In contrast, the Invention of Exhibit Ko 1 is not specified as such.

b. Different Feature 2

With regard to a composition (agent) for ophthalmic use, Present Invention 1 is specified as "a human conjunctival mast cell stabilizing agent for ophthalmic use". In contrast, the Invention of Exhibit Ko 1 is not specified as such.

c. Different Feature 3

Present Invention 1 is specified as "prepared as an eye drop". In contrast, the Invention of Exhibit Ko 1 is not specified as such.

(b) Different Features 1 and 2

Under the binding effect of the Previous Lawsuit Judgment, it is deemed that both of the matter specified as "in humans" (Different Feature 1) and the matter specified as "a human conjunctival mast cell stabilizing agent for ophthalmic use" (Different Feature 2) in Present Invention 1 would have been easily conceivable to a person ordinarily skilled in the art who had read Exhibits Ko 1 and 4.

(c) Different Feature 3

An eye drop is a dosage form commonly used as a topically administrable formulation in the field of ophthalmology. Therefore, the matter specified as "prepared as an eye drop" in Present Invention 1 is merely a design matter.

(d) Effect Achieved by Present Invention 1

a. Table 1 of the present description shows experimental results which compare stabilizing effects of human conjunctival mast cells by comparing inhibition rates of histamine release from human conjunctival mast cells. Cromolyn sodium and nedocromil sodium as disclosed in Table 1 are compounds which were widely known to a person ordinarily skilled in the art at the time of the priority date of the present case as compounds having mast cell stabilizing actions.

Among the experimental results as shown in Table 1, inhibition rates of histamine release obtained after treatment of human conjunctival mast cells with each of the above compounds 15 minutes before anti-human IgE stimulation are compared. As for cromolyn sodium, an inhibition rate reached a maximum value of 10.6% at a dose of 10 μM. However, the inhibition rate decreased with further dose (concentration) increase, and the inhibition rate became a negative value at doses of 100 μM or more; that is, a phenomenon of promoting histamine release occurred. In addition, as for nedocromil sodium, an inhibition rate reached a maximum value of 28.2% at a dose of 100 μM. However, the inhibition rate decreased with further dose (concentration) increase, decreasing to 7.2% at a dose of 1000 μM.

In contrast, as for the present compound, an inhibition rate of histamine release increased in a dose-dependent manner up to a high dose (high concentration) of 2000 μM, such as 29.6% at a dose of 300 μM, 47.5% at 600 μM, 66.7% at 1000 μM, and 92.6% at 2000 μM. That is, after the inhibition rate of histamine release reached a maximum value, a phenomenon of decreasing the inhibition rate of histamine release did not occur with further dose increase, in contrast to the case of cromolyn sodium and nedocromil sodium.

b. Exhibit Ko 1 discloses that when "an effect of each drug on histamine release from the conjunctiva caused by the antigen-antibody reaction was investigated", "KW-4679 was ineffective." Thus, Exhibit Ko 1 discloses that KW-4679 does not inhibit histamine release from the conjunctiva in guinea pigs; i.e., KW-4679 does not have a stabilizing action on conjunctival mast cells in guinea pigs.

In addition, "cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" and "trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" as

disclosed in Exhibit Ko 4 (Compound No. 20) correspond to the cis isomer and the trans isomer of the present compound, respectively. Further, Exhibit Ko 4 discloses that these compounds have a PCA inhibitory action in rats and that the PCA inhibitory action is considered to be based on an action of inhibiting release of a chemical mediator such as histamine from skin mast cell in rats.

Thus, Exhibit Ko 1 discloses the results of the experiments using conjunctival mast cells in guinea pigs, and Exhibit Ko 4 discloses the results of the experiments using skin mast cells in rats. However, neither Exhibit Ko 1 nor Exhibit Ko 4 discloses a result of an experiment using "conjunctival mast cells in humans."

The Previous Lawsuit Judgment held that it was common general technical knowledge at the time of the priority date of the present case that a histamine release inhibitory action of a drug on a mast cell may be different for different mast cell species or tissues, and that from an experimental result on a mast cell in one tissue of one animal species, it is not necessarily possible to predict an experimental result on a mast cell in another tissue of another animal species.

Taking the above common general technical knowledge into consideration, it cannot be deemed that an action of KW-4679 of Exhibit Ko 1 on human conjunctival mast cells could have been specifically predicted by a person ordinarily skilled in the art, on the basis of the results of the experiments using conjunctival mast cells in guinea pigs as disclosed in Exhibit Ko 1 and skin mast cells in rats as disclosed in Exhibit Ko 4.

In addition, according to the disclosure of Exhibit Ko 1, KW-4679 does not have a stabilizing action on conjunctival mast cells in guinea pigs. Thus, a person ordinarily skilled in the art could not have predicted that KW-4679 has a stabilizing action on human conjunctival mast cells.

Further, the "skin" mast cells in rats used in Exhibit Ko 4 are mast cells of a tissue which is different from the "conjunctiva". Furthermore, Exhibit Ko 4 does not disclose a result of an experiment using skin mast cells or conjunctival mast cells in rats to confirm an inhibitory effect of histamine release. Therefore, a person ordinarily skilled in the art could not have predicted that the compound of "Compound No. 20" in Exhibit Ko 4 (the cis isomer and the trans isomer of the present compound) has a stabilizing action on human conjunctival mast cells.

c. The experiment to investigate an inhibition rate of histamine release from human conjunctival mast cells in Exhibit Ko 39 (J. M. YANNI et al. "The In Vitro and In Vivo Ocular Pharmacology of Olopatadine (AL-4943A), an Effective Anti-Allergic / Antihistaminic Agent" Journal of Ocular Pharmacology and

Therapeutics Vol. 12, No. 4, pages 389-400, 1996) is an experiment using the same conditions as in the experiment in Table 1 of the present description.

Exhibit Ko 39 shows an inhibition rate of histamine release of AL-4943A (the cis isomer of the present compound) and ketotifen (Ketotifen as disclosed in Exhibit Ko 1) in Graph B of Figure 1. Exhibit Ko 39 discloses the experimental results showing that a concentration (dose) of AL-4943A increased in a dose-dependent manner even when the concentration (dose) of AL-4943A reached approximately 2000 μM, and that an inhibition rate of approximately 90% was maintained even when the concentration increased to 10000 μM, and that an IC_{50} value (a concentration at which an inhibition rate reaches 50%) was 559 ± 277 μM. These experimental results disclosed in Exhibit Ko 39, in which "a concentration (dose) of AL-4943A increased in a dose-dependent manner even when the concentration (dose) of AL-4943A reached approximately 2000 μM" and in which "an IC_{50} value (a concentration at which an inhibition rate reaches 50%) was 559 ± 277 μM" are both equivalent to the experimental results in Table 1 of the present description showing that the inhibition rate of histamine release in human conjunctival mast cells by the present compound increased in a dose-dependent manner up to 2000 μM and is 47.5% at 600 μM.

On the other hand, at the time of the priority date of the present case, ketotifen was an active ingredient in a drug which was available on the market for the treatment of allergic conjunctivitis as "Zaditen$^{(R)}$ Eye Drops Solution 0.05%". Ketotifen had been known for its pharmacological actions, including inhibition of PCA (Passive Cutaneous Anaphylaxis) reactions and inhibition of the release of chemical mediators such as histamine. In addition, Exhibit Ko 32 (SAKUMA Yasuko et al. "Sugi Kahunsho ni taisuru Ketotifen Tengan Yaku no Gan Yuhatu Hannou Yokusei Kouka (Inhibitory Effects of Ketotifen Eye Drops on Ocular-Induced Reaction to Cedar Pollen Allergy)", Ringan (Japanese Journal of Clinical Ophthalmology), Vol. 43, No. 8, Pages 1251-1254, 1989 (in Japanese)) discloses that according to measurement of histamine levels in tears of patients with cedar pollen allergy, "0.05% Ketotifen (HC) Eye Drops Solution" significantly achieved an inhibitory effect on histamine release as compared to "placebo eye drops solution", and this inhibitory effect on histamine release is considered to be a result of the inhibition of histamine release from mast cells which occurs after the induction of an allergic reaction by cedar antigen solution.

Thus, the results of the experiments with ketotifen disclosed in Exhibit Ko 39 merely confirm the significant inhibitory action of ketotifen on histamine release, which was known at the time of the priority date of the present case, by using "human

conjunctival mast cells".

According to the above, Exhibit Ko 39 is a publication distributed in 1996, which is after the priority date of the present case. However, the experimental results on the inhibition rate of histamine release by ketotifen and AL-4943A (the cis isomer of the present compound) on "human conjunctival mast cells" as disclosed in Exhibit Ko 39 are the experimental results which should be taken into consideration in determining the remarkable effect of Present Invention 1.

d. The present description shows in Table 1 that an inhibition rate of histamine release by the present compound on "human conjunctival mast cells" increases in a dose-dependent manner up to a high dose (high concentration) of 2000 μM, and that the maximum inhibition rate of histamine release (92.6% at 2000 μM) was significantly higher than the maximum values (10.6% and 28.2%) measured with the control drugs, cromolyn sodium and nedocromil sodium, respectively.

Thus, although Exhibit Ko 1 discloses that KW-4679 does not have a stabilizing action on conjunctival mast cells in guinea pigs, the present compound has a very high inhibition rate of histamine release on "human conjunctival mast cells". Therefore, it can be deemed that the present compound has a particularly remarkable effect which could not have been predicted by a person ordinarily skilled in the art.

On the other hand, Exhibit Ko 1 discloses that ketotifen as well as KW-4679 was "ineffective" in inhibiting histamine release from the conjunctiva in guinea pigs; i.e., ketotifen does not have a stabilizing action on conjunctival mast cells in guinea pigs.

According to the experimental results in Exhibit Ko 39, ketotifen also showed a remarkably high inhibition rate of histamine release on "human conjunctival mast cells" with a maximum value of approximately 90%, to the same extent as AL-4943A. However, ketotifen causes a rapid decrease in the inhibition rate of histamine release and severe histamine release at concentrations three times higher than the concentration (approximately 100 μM) which achieves the maximum inhibition rate of histamine release on "human conjunctival mast cells". In contrast, AL-4943A maintains a maximum inhibition rate of histamine release without decreasing even when reaching 10000 μM, which is a concentration several times the concentration (2000 μM) which achieves the maximum inhibition rate of histamine release on "human conjunctival mast cells."

According to these, it cannot be deemed that a person ordinarily skilled in the art could have predicted the experimental results showing that AL-4943A had a very broad range of concentrations as compared to ketotifen in achieving the maximum

inhibition rate of histamine release on "human conjunctival mast cells", even though ketotifen and KW-4679 were both treated equally as "ineffective" in inhibiting histamine release from the conjunctiva in guinea pigs in Exhibit Ko 1.

Further, the present description states that "the eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time. However, in more severe cases, the eye drops may be applied several times a day. A typical amount applied to the eyes is about 30 μl." The above statement means that the present compound, when applied to eye drops, not only has an effective effect with a small number of applications of twice a day, but also has an effective human conjunctival mast cell stabilizing effect without any particular difficulty even when a higher dose is administered by applying the eye drops several times a day if necessary. That is, the above statement means that the present compound has "high efficacy as a pharmaceutical."

Thus, it can be deemed that the experimental results shown in Exhibit Ko 39; i.e., "AL-4943A had a very broad range of concentrations in achieving the maximum inhibition rate of histamine release", are consistent with the fact that the present compound has "high efficacy as a pharmaceutical" as stated in the present description. In addition, it can be deemed that such experimental results are a particularly remarkable effect which could not have been predicted by a person ordinarily skilled in the art.

As mentioned above, the fact that the present compound has an excellent stabilizing effect (a high inhibition rate of histamine release) on "human conjunctival mast cells", and the fact that AL-4943A had a very broad range of concentrations in achieving the maximum inhibition rate of histamine release are both particularly remarkable effects which could not have been predicted by a person ordinarily skilled in the art from Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case. Such particularly remarkable effects should be taken into consideration in determining an inventive step as advantageous effects as compared to the Invention of Exhibit Ko 1.

B. Present Invention 2

Present Invention 2 adds to Present Invention 1 the matter "inhibits histamine release from a human conjunctival mast cell by 66.7% or more" for defining the invention. However, from Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case, it would have been very difficult for a person ordinarily skilled in the art to predict that the present compound "inhibits histamine release from a human conjunctival mast cell by 66.7%

or more". Thus, it cannot be deemed that Present Invention 2 would have been easily conceivable.

Further, as well as Present Invention 1, it can be acknowledged that an effect achieved by Present Invention 2 is a particularly remarkable effect which could not have been predicted by a person ordinarily skilled in the art from Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case.

C. According to the above, it cannot be deemed that it would have been easily conceivable to obtain the configuration of Present Invention 2 from Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case. In addition, each of the Present Inventions achieves advantageous effects as compared to the Invention of Exhibit Ko 1.

Therefore, it cannot be deemed that each of the Present Inventions could have been easily made by a person ordinarily skilled in the art on the basis of Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case.

(3) Reason 3 for Invalidation (Lack of Inventive Step Based on Exhibit Ko 3 as Primary Cited Document)

A. The Plaintiff asserts that Present Invention 1 and the Invention of Exhibit Ko 3 are common in that "a topically administrable ophthalmic composition (agent) for the treatment of allergic eye diseases (conjunctivitis) in humans, comprising a therapeutically effective amount of a specific oxepin derivative", and are different in Different Features 5 to 7 as follows.

(A) Different Feature 5

In Present Invention 1, an oxepin derivative is limited to "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid." In contrast, in the Invention of Exhibit Ko 3, the oxepin derivative is expressed as a generic concept including "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid". In Examples of Invention of Exhibit Ko 3, "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid" is exemplified.

(B) Different Feature 6

Present Invention 1 is specified as "a human conjunctival mast cell stabilizing agent for ophthalmic use". In contrast, the Invention of Exhibit Ko 3 is not specified as such.

(C) Different Feature 7

Present Invention 1 is specified as "prepared as an eye drop". In contrast, the Invention of Exhibit Ko 3 is merely specified as "an ophthalmic solution".

B. Different Feature 7

An eye drop is a dosage form commonly used as a topically administrable formulation in the field of ophthalmology. Therefore, the matter specified as "prepared as an eye drop" in Present Invention 1 is merely a design matter.

C. Different Feature 5

Exhibit Ko 3 discloses a compound represented by formula (I) in Markush form or a salt thereof, and further discloses that in formula (I), R^1 includes CH_2-O-, R^2 and R^3 each include C_1 alkyl, and R^4 includes a C_1 bivalent aliphatic hydrocarbon group which is bonded to the aromatic ring system at the 2-position. In addition, Exhibit Ko 3 discloses that the compound represented by formula (I) is believed to have anti-allergic activity and to inhibit the release of autacoids (histamine, serotonin, and the like) from mast cells and may be used for the symptomatic control of allergic conditions including allergic conjunctivitis, and that a formulation includes those suitable for ophthalmic administration.

Further, Exhibit Ko 3 discloses that (E)/(Z)11-(3-dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid was used as the specific compound to test an "anaphylactoid activity"; i.e., whether or not symptoms of respiratory distress were inhibited by challenge of an anaphylactoid inducing agent, compound 48/80, in rats. Furthermore, Exhibit Ko 3 discloses formulation examples including an ophthalmic solution.

However, Exhibit Ko 3 does not disclose a result of an experiment using the present compound of the present patent; i.e., 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid. Thus, it cannot be deemed that Exhibit Ko 3 discloses motivation to select "the present compound" of Different Feature 5 from the compounds represented by formula (I) in Markush form or salts thereof, and use "the present compound".

In addition, the system for testing an "anaphylactoid activity" disclosed in Exhibit Ko 3 evaluates inhibition of respiratory distress induced by an anaphylactoid inducing agent in rats, and does not evaluate an effect of inhibiting release of autacoids such as histamine from human conjunctival mast cells; i.e., an effect of stabilizing human conjunctival mast cells.

Further, Exhibit Ko 3 discloses that "The present compound is believed to inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and to inhibit directly the antigen-induced production of histamine." However,

Exhibit Ko 3 does not show the results of the experiments specifically confirming the effect of inhibiting autacoid release from mast cells. Thus, the above disclosure of Exhibit Ko 3 merely indicates an assumption, and the effect of stabilizing mast cells is not specifically disclosed in Exhibit Ko 3. Furthermore, in view of the common general technical knowledge on mast cell heterogeneity at the time of the priority date of the present case (the above (2)A(D)b), it cannot be deemed that a stabilizing effect on "human conjunctival mast cells" is disclosed in Exhibit Ko 3 on the basis of the results of the experiments based on the test system for the "anaphylactoid activity" using rats as disclosed in Exhibit Ko 3.

Thus, taking the disclosure of Exhibit Ko 4 into consideration, even if it would have been easily conceivable to replace the active compound disclosed in Formulation Examples of Exhibit Ko 3 (Compound No. 3 in Exhibit Ko 4) with "the present compound (Compound No. 20 in Exhibit Ko 4)" of Different Feature 5 on the basis of the fact that "Compound No. 20 (the present compound)" of Exhibit Ko 4 has the same or a slightly superior anti-allergic action to "Compound No. 3 (the active compound disclosed in Formulation Examples of Exhibit Ko 3)" of Exhibit Ko 4, it cannot be deemed that it would have been easy to make the invention of Exhibit Ko 3 to be "a human conjunctival mast cell stabilizing agent for ophthalmologic use" of Different Feature 6, since the stabilizing effect on "human conjunctival mast cells" is not disclosed in Exhibit Ko 3.

D. Different Feature 6

As mentioned in the above C, a person ordinarily skilled in the art who had read the disclosure of Exhibit Ko 4 could not have predicted that the compound of "Compound No. 20" of Exhibit Ko 4 (the present compound) has a stabilizing action on human conjunctival mast cells. Thus, it cannot be deemed that it would have been easy to make the invention of Exhibit Ko 3 to be "a human conjunctival mast cell stabilizing agent for ophthalmologic use" of Different Feature 6 on the basis of the disclosure of Exhibit Ko 4.

In addition, a person ordinarily skilled in the art who had read the disclosure of Exhibit Ko 1 could not have predicted that KW-4679 of Exhibit Ko 1 (the cis isomer of the present compound) has a stabilizing action on human conjunctival mast cells. Thus, it cannot be deemed that it would have been easy to make the invention of Exhibit Ko 3 to be "a human conjunctival mast cell stabilizing agent for ophthalmologic use" of Different Feature 6 on the basis of the disclosure of Exhibit Ko 1.

Even if the motivation to select the present compound from the compounds

shown in Formula (I) in Markush form in Exhibit Ko 3 or salts thereof, and to apply the present compound to the use of "a human conjunctival mast cell stabilizing agent" is not denied in view of the descriptions in Exhibit Ko 4 and Exhibit Ko 1, the effects achieved by each of the Present Inventions are particularly remarkable effects which could not have been predicted by a person ordinarily skilled in the art from Exhibit Ko 3, Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case. Such particularly remarkable effects should be taken into consideration as advantageous effects as compared to the Invention of Exhibit Ko 3 in determining an inventive step.

E. As mentioned above, it cannot be deemed that it would have been easily conceivable to obtain each of the Present Inventions from Exhibit Ko 3, Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case. Even if it would have been easily conceivable, each of the Present Inventions achieves advantageous effects as compared to the Invention of Exhibit Ko 3.

Therefore, it cannot be deemed that each of the Present Inventions could have been easily made by a person ordinarily skilled in the art on the basis of Exhibit Ko 3, Exhibit Ko 1, Exhibit Ko 4, and the common general technical knowledge at the time of the priority date of the present case.

(omitted)

No. 5 Judgment of This Court

1. Each of the Present Inventions

(1) Claims 1 and 5 in the Scope of Claims after the Second Correction concerning each of the Present Inventions is as mentioned in the above No. 2, 2. The statement of the present description is as follows (Exhibit Ko 205).

A. Field of the Invention

The present invention relates to topical ophthalmic formulations used for treating allergic eye diseases, such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. More particularly, the present invention relates to therapeutic and prophylactic topical use of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for treating and/or preventing allergic eye diseases.

(Page 3, lines 3 to 9)

B. Description of the Related Art

As taught in U.S. Patent No. 4,871,865 and No. 4,923,892 ... ("Burroughs Wellcome Patents"), certain carboxylic acid derivatives of doxepin, including 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2(E)-acrylic acid, have antihistaminic and antiasthmatic activity. These two patents classify the carboxylic acid derivatives of doxepin as mast cell stabilizers with antihistaminic action. ...

Although both of the Burroughs Wellcome Patents claim that the variety of pharmaceutical formulations disclosed are effective for both veterinary and human medical use, neither patent contains an example demonstrating that the carboxylic acid derivatives of doxepin have activity in humans.

However, it is now well established that the types of mast cells which exist in rodents are different from those in humans. ... Moreover, mast cell populations exist within the same species that differ in phenotype, biochemical properties, functional and pharmacological responses, and ontogeny. These recognized differences in mast cells both between and within species are referred to as mast cell heterogeneity. ... Because different mast cells exhibit different responses to pharmacological agents, it is not obvious that compounds claimed to be anti-allergic agents ("mast cell stabilizing agents") will have clinical utility in specific mast cell populations. The assumption that mast cells are a homogeneous population and that therefore the effects of anti-allergic drugs observed in experiments in rat mast cells would have been predictive of those in human cells is known to be incorrect.
(Page 3, line 10 to page 4, line 18)

Topical ophthalmic formulations which contain drugs having conjunctival mast cell activity may only need to be applied once every 12 to 24 hours instead of once every 2 to 4 hours. One disadvantage to the ophthalmic use of reported anti-allergic drugs which in fact have no human conjunctival mast cell stabilizing activity is an increased dosage frequency. Because the effectiveness of ophthalmic formulations containing drugs which do not have conjunctival mast cell activity stems primarily from a placebo effect, more frequent doses are typically required than for drugs which do exhibit conjunctival mast cell activity. ...

What is needed are topically administrable drug compounds that have demonstrated stabilizing activity on mast cells obtained from human conjunctiva, the target cells for treating allergic eye diseases.
(Page 5, lines 10 to page 6, line 5)

C. Summary of the Invention

The present invention provides a method for treating an allergic eye disease characterized by administering to the eye a topical ophthalmic formulation. This topical ophthalmic formulation contains a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (hereinafter referred to as Compound A) or a pharmaceutically acceptable salt thereof. The formulation may contain the cis isomer of Compound A (Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), the trans isomer of Compound A (E-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), or a combination of both the cis and the trans isomers of Compound A, and unless specified otherwise, "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" or "Compound A" means the cis isomer, the trans isomer, or a mixture of the two. …

Compound A has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases. In addition to its mast cell stabilizing activity, Compound A also possesses significant antihistaminic activity. Thus, in addition to a prophylactic effect, Compound A will also have a therapeutic effect.

(Page 6, lines 7 to 29)

D. Detailed Description of the Invention

Compound A is a known compound and both the cis and the trans isomers of Compound A can be obtained by the methods disclosed in U.S. Patent No. 5,116,863 ... .

The inhibitory effects of reported anti-allergic, mast cell stabilizing drugs on mast cells obtained from human conjunctiva (the target cells for topical ophthalmic drug preparations claimed useful in treating allergic conjunctivitis) were tested according to the following experimental method. Human conjunctival tissues ... were weighed and transferred to petri dishes containing culture medium... and equilibrated ... Test compounds were administered to the mast cell cultures either 1 or 15 minutes before stimulation with anti-human IgE. Inhibition of histamine release resulting from challenge of drug treated mast cells was determined by direct comparison with histamine release from vehicle treated, anti-IgE challenged mast cells ... . The results are reported in Table 1 below.

As Table 1 clearly shows, the anti-allergic drugs disodium cromoglycate and nedocromil failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, Compound A (cis isomer) produced concentration-dependent inhibition of

mast cell degranulation.
(Page 7, line 1 to page 9, line 7)

Table 1

Effect of Compound on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Cromolyn sodium	1000	15	-15.4
	300	15	-6.9
	100	15	-1.2
	30	15	1.8
	10	15	10.6
Cromolyn sodium	1000	1	-9.4
	300	1	-1.8
	100	1	1.2
	30	1	0.1
	10	1	-0.9
Nedocromil sodium	1000	15	7.2
	300	15	11.3
	100	15	28.2*
	30	15	15.2
	10	15	9.2
	3	15	13.2
	1	15	10.7
	0.3	15	3.7
	0.1	15	8.7
Nedocromil sodium	1000	1	-1.1
	300	1	4.0
	100	1	6.7
	30	1	-0.9
	10	1	-6.5
	3	1	0.8
	1	1	4.8
	0.3	1	8.8
	0.1	1	17.4
Compound A	2000	15	92.6*
	1000	15	66.7*
	600	15	47.5*
	300	15	29.6*
	100	15	13.0
	30	15	-3.9

*p<0.05, Dunnett's t-test

Compound A may be administered to the eye by means of conventional topical ophthalmic formulations, such as solutions, suspensions, or gels. The preferred formulation for topical ophthalmic administration of Compound A is a solution. The solution is administered as eye drops. The preferred form of Compound A in the topical ophthalmic formulations of the present invention is the cis isomer. A general method of preparing the eye drops of the present invention is stated below.

Compound A and an isotonic agent are added to sterilized purified water, and if

required, a preservative, a buffering agent, a stabilizing agent, a viscous vehicle, and the like are added to the solution and dissolved therein. The concentration of Compound A is 0.0001 to 5 w/v%, preferably 0.001 to 0.2 w/v%, and most preferably about 0.1 w/v%, based on the sterilized purified water. After dissolution, the pH is adjusted with a pH controller to be within a range which allows use as an ophthalmologic medicine, preferably within the range of 4.5 to 8. ...

The eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time. However, in more severe cases, the eye drops may be applied several times a day. A typical amount applied to the eyes is about 30 μl.

(Page 13, line 1 (except for Table part) to page 14, line 13)

(2) According to the above (1), it can be acknowledged that each of the Present Inventions is as follows.

A. Each of the Present Inventions relates to therapeutic and prophylactic topical use of the present compound for treating and/or preventing allergic eye diseases (the above (1)A).

B. The present compound has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases. In addition to its mast cell stabilizing activity, the present compound also possesses significant antihistaminic activity. Therefore, the present compound has a therapeutic effect in addition to a preventive effect. (the above (1)C)

C. The inhibitory effects of anti-allergic, mast cell stabilizing drugs on mast cells obtained from human conjunctiva were tested. As a result, the anti-allergic drugs disodium cromoglycate and sodium nedocromil (it can be acknowledged that "ネドクロシルナトリウム" stated in the present description is a clerical error of "ネドクロミルナトリウム" (sodium nedocromil)) failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, the present compound (cis isomer) produced concentration-dependent inhibition of mast cell degranulation (Table 1) (the above (1)D).

D. A general method of preparing the eye drops of each of the Present Inventions is as follows: the present compound and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizing agent, a viscous vehicle, and the like are added to the solution and dissolved therein. The concentration of the present compound is 0.0001 to 5 w/v%, preferably 0.001 to 0.2 w/v%, and most preferably about 0.1 w/v%, based on the sterilized purified water. After dissolution, the pH is adjusted with a pH controller to

be within a range which allows use as an ophthalmologic medicine, preferably within the range of 4.5 to 8. (the above (1)D)

E. The eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time. However, in more severe cases, the eye drops may be applied several times a day. A typical amount applied to the eyes is about 30 μl. (the above (1)D)

2. Reason 1 for Rescission (Reason 2 for Invalidation: Erroneous Determinations of Inventive Step Based on Invention of Exhibit Ko 1)

(1) Invention of Exhibit Ko 1

A. Exhibit Ko 1 discloses as follows.

(A) Title

Effects of Anti-allergic Drugs on Experimental Allergic Conjunctivitis in Guinea Pigs

(B) Abstract

Effects of various anti-allergic drugs on antigen-induced and histamine-induced conjunctivitis were studied using guinea pigs. As a result, eye drops of chlorpheniramine, ketotifen, and KW-4679 showed a more potent inhibitory effect on histamine-induced conjunctivitis than on antigen-induced conjunctivitis.
(Abstract part, lines 1 to 3)

(C) Introduction

Drugs with antihistaminic action, such as chlorpheniramine and ketotifen, are widely used in the treatment of allergic conjunctivitis. Previously, the authors found that prominent conjunctivitis was induced in guinea pigs by applying antigen and histamine to the eye.
(Page 603, left column, lines 1 to 6)

(D) I. Experimental Method

1. Induction of Conjunctivitis

In the experiment, ... guinea pigs ... five individuals in one group were used. ...

2. Quantification of Conjunctivitis Symptoms

The degree of conjunctivitis was defined as follows.

Score 1: Mild hyperemia is shown.

Score 2: Severe hyperemia is shown.

Score 3: Mild to moderate edema in addition to hyperemia is shown.

Score 4: Prominent edema is shown.

3. Histamine Release from Conjunctiva

Fifteen minutes after applying an antigen to the eye, the conjunctiva was

excised, weighed, and washed with saline solution. Then, it was homogenized ..., centrifuged ..., and the supernatant was cryopreserved. Thereafter, ... the supernatant was thawed and centrifuged, and a histamine content of the supernatant was determined by HPLC (High Performance Liquid Chromatography).

4. Measurement of Histamine Content in Tear Fluid

Fifteen minutes after applying an antigen to the eye, saline solution was applied to the eye, and then collected and ... centrifuged, and a histamine content of the supernatant was determined by HPLC.

(Page 603, right column, line 1 to page 604, right column, line 2)

(E) II. Experimental Results

1. Effects on Antigen-induced Conjunctivitis

Effects of various anti-allergic drugs on allergic conjunctivitis induced by applying an antigen solution (20 mg/ml) to the conjunctiva in sensitized guinea pigs are shown in Figure 1. Chlorpheniramine showed a concentration-dependent inhibitory action with eye drops of 10 to 100 ng/μl, and a significant difference was observed at concentrations of 50 and 100 ng/μl. Ketotifen, ... and KW-4679 showed significant inhibitory actions at concentrations of 10 and 100 ng/μl. Amelexanox also showed significant differences at concentrations of 2500 and 5000 ng/μl.

2. Effects on Antigen-induced and Histamine-induced Conjunctivitis

Table 1 shows the effects of various anti-allergic drugs on antigen-induced and histamine-induced conjunctivitis, with IC_{50} values. Chlorpheniramine, ketotifen, and KW-4679 inhibited histamine-induced conjunctivitis more potently than they inhibited antigen-induced conjunctivitis. ... Amelexanox inhibited antigen-induced conjunctivitis but was ineffective in histamine-induced conjunctivitis.

3. Actions on Histamine Release from Conjunctiva

The results showed that ... amelexanox (2500 ng/ml) significantly inhibited histamine release from the conjunctiva, as shown in Figure 2. The effects of chlorpheniramine, ketotifen, and KW-4679 were not significant.

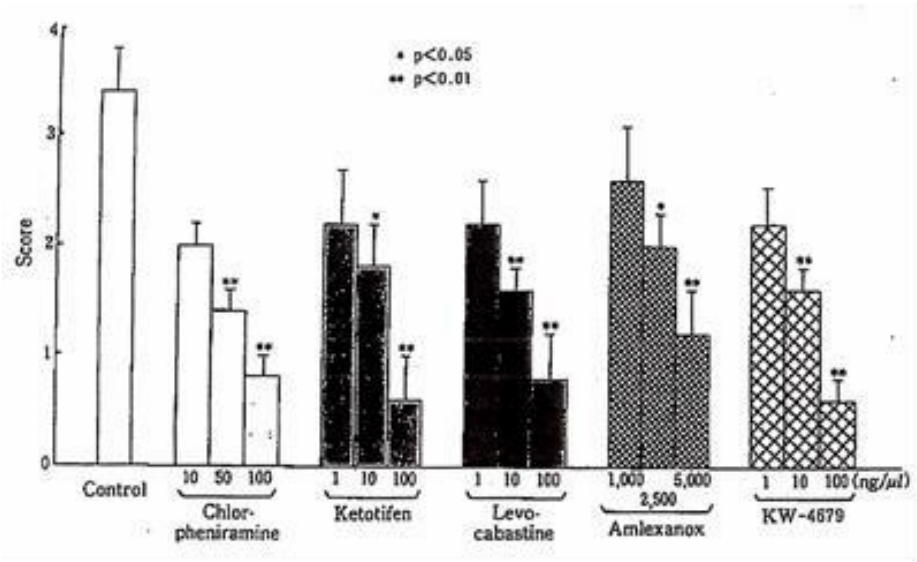
4. Effects on Histamine Content of Tear Fluid

Before applying an antigen to the eye, a histamine content of the tear fluid in guinea pigs was 1.7 ± 0.4 ng/ml, but after applying the antigen to the eye, the histamine content increased by a factor of approximately five times (8.6 ± 0.8 ng/ml). ... When amelexanox was applied to the eye 15 minutes before the antigen was applied, the increase in the histamine content of the tear fluid caused by the antigen-antibody reaction was significantly reduced. Chlorpheniramine, ketotifen, and KW-4679 did not show significant effects.

(Page 604, right column, line 3 to page 605, left column, line 19)

(F) Figure 1

Figure 1 Effects of Anti-Allergic drugs on Conjunctivitis Caused by Antigen-Antibody Reactions



(G) Table 1

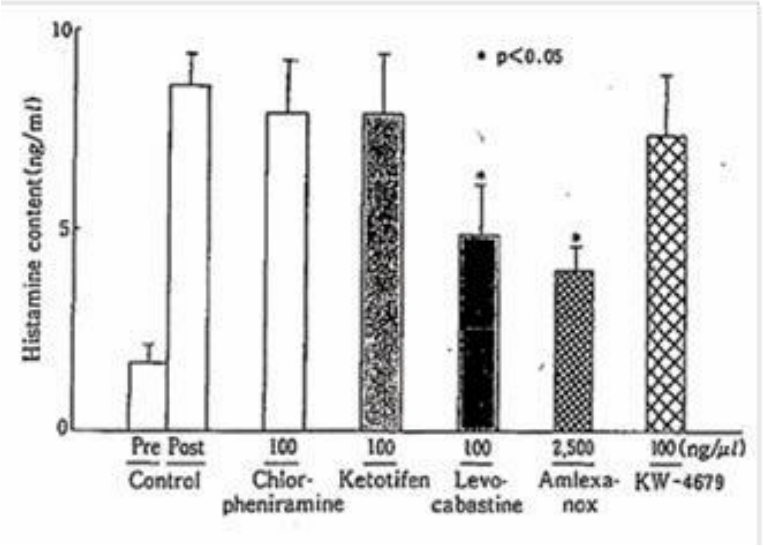
Table 1 Effects of Anti-Allergic Drugs on Antigen-induced and Histamine-induced Conjunctivitis (IC_{50})

Table 1 Effects of Anti-Allergic Drugs on Antigen-induced and Histamine-induced Conjunctivitis (IC_{50})

Drugs	IC_{50} values (ng/μl)	
	Antigen	Histamine
Chlorpheniramine	18.4	11.2
Ketotifen	4.12	2.82
Levocabastine	4.14	7.67
Amlexanox	2,767	>5,000
KW-4679	3.90	2.44

(H) Figure 2

Figure 2 Effects of Anti-Allergic Drugs on Increasing Histamine Content of Tear Fluid Caused by Antigen-Antibody Reactions



(I) III. Discussion

The results of this study show that chlorpheniramine, ketotifen, and KW-4679 had a more potent effect on histamine-induced conjunctivitis than on antigen-induced conjunctivitis. ... On the other hand, amlexanox showed a positive effect on antigen-induced conjunctivitis, but was ineffective against histamine-induced conjunctivitis. These findings suggest that chlorpheniramine, ketotifen, and KW-4679 may have suppressed conjunctivitis caused by the antigen-antibody reaction, mainly due to the antihistaminic action of these drugs. On the other hand, levocabastine and amlexanox may inhibit histamine release from the conjunctiva caused by the antigen-antibody reaction. Then, an effect of each drug on histamine release from the conjunctiva caused by the antigen-antibody reaction was investigated, and both drugs showed significant inhibitory effects. Chlorpheniramine, ketotifen, and KW-4679 were ineffective.

(Page 605, left column, lines 20 to 34)

B. Invention of Exhibit Ko 1

According to the evidence (Exhibits Ko 2-1 and -2) and the entire import of the oral argument, it can be acknowledged that KW-4679 is hydrochloride of "Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" (hydrochloride of the Z form [cis isomer] of the present compound), and KW-4679 corresponds to "a pharmaceutically acceptable salt" of "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" (the present compound) in Present Invention 1, and KW-4679 corresponds to "(Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" (the cis

isomer of the present compound) in Present Invention 2.

Further, according to the above A, it can be acknowledged that Exhibit Ko 1 discloses the results of experiments using eye drops containing anti-allergic drugs such as Amelexanox, Chlorpheniramine, Ketotifen, and KW-4679 (hydrochloride of the cis isomer of the present compound), and that in the experiments using guinea pigs, the application of chlorpheniramine, Ketotifen, and KW-4679 to the eye showed more potent inhibitory effects on histamine-induced conjunctivitis than on antigen-induced conjunctivitis, but showed no significant effects on histamine release from the conjunctiva.

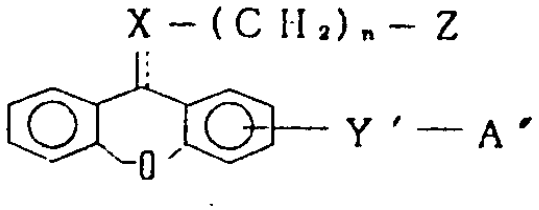
(2) Invention of Exhibit Ko 4

Exhibit Ko 4 discloses as follows.

A. Scope of Claims

...

(2) An anti-allergic agent comprising, as an active ingredient, a dibenz[b,e]oxepin derivative represented by the formula



(wherein: X represents =N-, =CH-, or $-CH_2-$; n represents 0, 1, 2, 3, or 4; and Z represents a 4-methylpiperazino group, a 4-methylhomopiperazino group, a piperidino group, a pyrrolidino group, a thiomorpholino group, a morpholino group, or $-NR_6R_7$ (wherein R_6 and R_7 are the same or different and represent a hydrogen atom or a lower alkyl group); ⎓ represents a single bond or a double bond; when X is =CH- or $-CH_2-$, -Y'-A" represents -Y-A (wherein: A represents a hydroxymethyl group, a lower alkoxymethyl group, a triphenylmethyloxymethyl group, a lower alkanoyloxymethyl group, a lower alkanoyl group, a carboxy group, a lower alkoxycarbonyl group, a triphenylmethyloxycarbonyl group, $-CONR_1R_2$ (wherein R_1 and R_2 are the same or different and represent a hydrogen atom or a lower alkyl group), a 4,4-dimethyl-2-oxazolin-2-yl group, or -CONHOH; and Y represents $-(CH_2)_m-$, $-CHR_3-(CH_2)_m-$, or $-CR_4=CR_5-(CH_2)_m-$, which is substituted at the 2-position or 3-position of the mother nucleus (wherein: R_3 represents a lower alkyl group; R_4 and R_5 are the same or different and each represent a hydrogen atom or a lower alkyl group; and m represents

0, 1, 2, 3, or 4), wherein the left side of each formula as defined above is bound to the mother nucleus), and when X is =N-, -Y'-A" represents -Y-A wherein Y is bonded to the 2-position of the mother nucleus (wherein Y and A has the same meanings as defined above)), or a pharmacologically acceptable salt thereof.

...

B. Detailed Description of the Invention

(A) The present invention relates to a novel dibenz[b,e] oxepin derivative and an anti-allergic agent or an anti-inflammatory agent containing the same as an active ingredient.

(Page 2, left lower column, lines 3 to 5)

(B) Table 1 shows specific examples of the compound (I) or a pharmacologically acceptable salt thereof obtained by each producing method and Table 2 shows the structures thereof.

(Page 8, right upper column, line 6 (except for the chemical formula part) to line 8)

(C) Table 1

a. Compound No. 3

Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid

b. Compound No. 20

Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

c. Compound No. 3'

1/2 Fumarate-1/5 hydrate of Compound 3 (trans form 99%)

d. Compound No. 20'

Fumarate-3/2 hydrate of Compound 20 (trans form 95%)

(D) Test for anti-allergic action

Anti-allergic action was investigated by a homologous PCA (passive cutaneous anaphylaxis) test of rats for 48 hours. As experimental animals, Wistar male rats having body weights of 180 to 220 g were used for sampling of antiserum, and Wistar male rats having body weights of 120 to 140 g were used for the PCA test.

A) Preparation of anti EWA rat serum

...

B) Homologous PCA test of rats for 48 hours

Groups each consisting of 3 rats were used, and 0.05 ml of anti-EWA rat serum diluted 8-fold with a physiological saline solution was incutaneously injected each at two positions of depilated back to make the animals passively sensitized. After 47 hours, the compound of the present invention, or its solution (physiological saline solution or CMC solution) was orally administered. One hour thereafter, 0.5 ml/100 g of 1% Evan's blue physiological saline solution containing 2 mg of the antigen EWA was administered into the tail vein, and 30 minutes thereafter, the animals were sacrificed by exsanguination. Then, the skins were stripped and the amount of leaked pigment at the blue-dyed parts was measured according to the method of Katayama et al. [Microbiol. Immunol. 22, 89 (1978)]. That is, the blue-dyed parts were cut out by scissors, and placed in test tubes containing 1 ml of 1 N KOH and incubated at 37°C for 24 hours. Then, 9 ml of a mixture of 0.6 N phosphoric acid and acetone (5:13) was added thereto, and the mixture was shaken and centrifuged at 2500 rpm for 10 minutes. Absorbancy of the supernatant at 620 μm was measured, and the amount of leaked pigment was quantitatively determined by the calibration curve prepared in advance. An average of measurements at the two position was made a value for one individual, and an inhibition rate for each individual was calculated by the following formula:

Inhibition rate (%) =

$$\left(\frac{\text{Average leaked amount of solvent-administered group} - \text{Leaked amount of test compound-administered group}}{\text{Average leaked amount of solvent-administered group}}\right) \times 100$$

Note that the cases where the inhibition rate is 50% or more were regarded as a positive PCA inhibitory action, and a minimum administered dosage where a positive case was observed in at least one of three individuals was regarded as a minimum effective dosage (MED). The results are shown in Table 5.

(Page 13, left lower column, line 3 from the bottom to page 14, left upper column, line 7 from the bottom)

(E) Table 5

Compound No.	Acute Toxicity (M.L.D) mg/kg po	Acute Toxicity (M.L.D) mg/kg ip	Anti-allergic Action: Number of Positive Individuals in One Group of Three Individuals 100	10	1	0.1	0.01	Dosage 0.001	MED mg/kg
3 (Cis)	>300	>100	3/3	3/3	3/3	3/3	0/3	—	0.1
3' (Trans)	>300	>100	3/3	2/3	1/3	1/3	0/3	—	0.1
20' (Trans)	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
20 (Trans)	>300	>100	2/3	2/3	3/3	3/3	0/3	0/3	0.1
20 (Cis)	>300	>100	3/3	3/3	3/3	3/3	1/3	0/3	0.01

(F) ... Compound (I) and a pharmacologically acceptable salt thereof have a PCA inhibitory action and/or carageenin paw edema inhibitory action. The PCA inhibitory action is considered to be based on an action inhibiting release of a chemical mediator such as histamine from skin mast cell. Therefore, Compound (I) and a pharmacologically acceptable salt thereof are considered to be useful for treating an allergic disease such as bronchus asthma which is caused by a trachea contractile action of the chemical mediator such as histamine.

(Page 15, right upper column, line 1 (except for Table part) to line 10)

(3) Common General Technical Knowledge at the Time of the Priority Date of the Present Case

A. Common General Technical Knowledge on Research and Development of Drugs for Inhibiting Human Allergic Conjunctivitis

(A) Anti-allergic drugs can be broadly classified into two categories according to their mechanism of action: drugs which have an antagonistic action against various chemical mediators such as histamine which is produced and released from mast cells; and drugs which have an inhibitory action on the release of these chemical mediators from mast cells (Exhibits Ko 12, 30, and 31). In research and development of drugs for inhibiting human allergic conjunctivitis, these two actions were also generally confirmed (Exhibits Ko 7, 10, 12, 20, 23, 30 to 32, 41, and 42).

(B) In the research and development of drugs for inhibiting human allergic

conjunctivitis, animal models of conjunctivitis in rats and guinea pigs, which are similar to human allergic conjunctivitis, have been developed and used to evaluate effects of drugs such as eye drops (Exhibits Ko 13 to 18, 41, and 42).

The package insert of the human anti-allergic ophthalmic eye drop which was marketed at the time of the priority date of the present case stated in the column of "Drug Effects and Pharmacology" that each active ingredient suppressed conjunctivitis in a rat and guinea pig model of animal conjunctivitis and inhibited the release of chemical mediators, such as histamine, from rat abdominal cavity mast cells, etc. (Exhibits Ko 7, 10, and 23).

(with regard to the above (A) and (B), page 83, line 18 to page 84, line 15 of the Previous Lawsuit Judgment [Exhibit Ko 84])

B. Mast Cell Heterogeneity

(A) At the time of the priority date of the present case, it was common general technical knowledge that a histamine release inhibitory action of drugs on mast cells may be different for different mast cell species or tissues, and that from results of experiments on mast cells in one tissue of one animal species, it is not necessarily possible to predict results of experiments on mast cells in other tissues of other animal species (Exhibits Ko 101 to 103 and 127 to 129).

(B) However, according to the facts in the above A(B), it cannot be denied that results of experiments on drug responses in animal conjunctivitis models of rats and guinea pigs and on drug responses in human conjunctivitis may show similar trends, or that results of experiments on mast cells in one tissue of rats and guinea pigs and on mast cells in human conjunctiva may show similar trends. Thus, with regard to mast cell heterogeneity, it can only be deemed that results of experiments on mast cells in one tissue of one animal species cannot necessarily predict experimental results of mast cells in other tissues of other animal species.

(with regard to the above (A) and (B), page 84, line 16 to page 86, line 3 and page 87, lines 5 to 12 of the Previous Lawsuit Judgment [Exhibit Ko 84])

(4) The Previous Lawsuit Judgment determined that, based on the common general technical knowledge as mentioned in the above (3), it should be deemed that a person ordinarily skilled in the art who had read Exhibits Ko 1 and 4 would have been motivated to attempt to apply an eye drop containing KW-4679 (hydrochloride of the cis isomer of the present compound) for inhibiting allergic conjunctivitis as disclosed in Exhibit Ko 1 to an eye drop for allergic eye diseases in humans. The Previous Lawsuit Judgment further determined that in attempting to apply KW-4679 as mentioned above, the person ordinarily skilled in the art would have been motivated

to confirm that KW-4679 has an antagonistic action on histamine, etc. which is produced and released from human conjunctival mast cells, as well as to confirm that KW-4679 has an inhibitory action on the release of histamine from human conjunctival mast cells. For such reasons, the Previous Lawsuit Judgment determined that it can be acknowledged that it would have been easily conceivable to confirm that KW-4679 has an inhibitory action on the release of histamine from human conjunctival mast cells (an "human conjunctival mast cell stabilizing" action) and to apply KW-4679 to the use of a "human conjunctival mast cell stabilizing agent." Then, based on that determination, the Previous Lawsuit Judgment determined that the Second Trial Decision erred in determining that "it cannot be deemed that the matter 'human conjunctival mast cell stabilizing' for defining the invention in each of the Present Inventions would have been motivated from the disclosures of Exhibits Ko 1 and 4, and that therefore, the reason for invalidation asserted by the Plaintiff; i.e., lack of an inventive step based on Exhibit Ko 1 as the primary cited document, is unfounded."

As mentioned above, the Previous Lawsuit Judgment determined that with regard to each of the Present Inventions, there would have been a motivation to arrive at the configuration of the invention. In this regard, even when there would have been a motivation to arrive at the configuration of the invention, in the case where an effect of the invention is remarkable to the extent that the effect of the invention exceeds the effect that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention at the time of the priority date, it cannot be acknowledged that such invention could have been easily made by a person ordinarily skilled in the art. The Previous Lawsuit Judgment did not determine to the extent of whether or not each of the Present Inventions has such an unpredictable and remarkable effect, and therefore, it is construed that the binding effect of the Previous Lawsuit Judgment (Article 33, paragraph (1) of the Administrative Case Litigation Act) does not extend to this issue.

Accordingly, it will be determined whether or not each of the Present Inventions has such an unpredictable and remarkable effect.

(5) Present Invention 1

A. According to the present description, in the experiment stated in the present description (the experiment to measure an inhibition rate of histamine release from human conjunctival mast cells by administering a drug to a cultured cell population), it can be acknowledged that: the present compound showed an inhibition rate of histamine release from human conjunctival mast cells of 29.6% at 300 μM,

47.5% at 600 μM, 66.7% at 1000 μM, and 92.6% at 2000 μM; that is, the inhibition rate increased as the concentration increased in the range from 30 μM to 2000 μM, and the present compound showed a high inhibition rate of histamine release of 66.7% at 1000 μM and maintained a high inhibition rate of 92.6% at 2000 μM, which is twice as high as 1000 μM; and that in contrast, disodium cromoglycate (cromolyn sodium), which is an anti-allergic drug, showed an inhibitory effect on histamine release of 10.6% at 10 μM and 1.8% at 30 μM at the same treatment time, but it could not significantly inhibit histamine release at 100 μM, 300 μM, and 1000 μM; and that nedocromil sodium, which is another anti-allergic drug, showed no concentration-dependent change in the range up to 1000 μM at the same treatment time, and only showed a maximum inhibition rate of histamine release of 28.2% at 100 μM.

According to these, as an effect of the present compound in Present Invention 1, it can be acknowledged that an inhibition rate of histamine release from human conjunctival mast cells increased in a concentration-dependent manner between 30 μM and 2000 μM, to a maximum value of 92.6%, and between these concentrations, unlike cromolyn sodium and nedocromil sodium, a phenomenon of decreasing the inhibition rate did not occur with higher doses (concentrations) than the dose (concentration) at which the maximum inhibition rate was reached.

B.(A) First of all, with regard to the present compound, there is no evidence that it can be acknowledged that it was clear at the time of the priority date of the present case that the inhibition rate of histamine release from human conjunctival mast cells increased in a concentration-dependent manner between 30 μM and 2000 μM, to a maximum value of 92.6%, and between these concentrations, a phenomenon of decreasing the inhibition rate did not occur with higher doses (concentrations) than the dose (concentration) at which the maximum inhibition rate was reached.

(B) Next, it will be determined whether or not the effects of the present compound could have been predicted from the effects of ketotifen.

a. According to Exhibit Ko 1, both Ketotifen (ketotifen) and KW-4679 (hydrochloride of the cis isomer of the present compound) have been evaluated as not having a significant inhibitory effect on histamine release from the conjunctiva in guinea pigs. However, Exhibit Ko 32 discloses that effects of Ketotifen (HC) (ketotifen) eye drop solution on histamine release were studied in the eyes of patients with cedar pollen allergy, and that amounts of histamine in tear fluids at 5 and 10 minutes after the induction of an allergic reaction showed significant inhibitory effects on histamine release as compared to those in the control eye, and that the inhibition rates of histamine release were 67.5% at 5 minutes after the induction and

67.2% at 10 minutes after the induction.

Accordingly, it can be acknowledged that ketotifen has application as a human conjunctival mast cell stabilizing agent in humans, in contrast to the results of experiments in guinea pigs (Exhibit Ko 1), where the inhibition rate of histamine release was 67.5% at 5 minutes after the induction and 67.2% at 10 minutes after the induction. However, there is no evidence that it can be acknowledged that, at the time of the priority date of the present case, it was clear whether or not ketotifen has a concentration-dependent effect on an inhibition rate of histamine release from human conjunctival mast cells between 30 μM and 2000 μM.

Note that Exhibit Ko 39 is a publication which was published after the priority date of the present case, and thus, by taking the disclosure of Exhibit Ko 39 into consideration, it cannot be acknowledged that ketotifen has an effect beyond what has been found above.

b. There is no evidence that it can be acknowledged that it was known to a person ordinarily skilled in the art at the time of the priority date of the present case that Chlorpheniramine (chlorpheniramine), which is stated in Exhibit Ko 1 as not having an inhibitory effect on histamine release in the conjunctiva in guinea pigs as well as Ketotifen (ketotifen) and the present compound, has a stabilizing effect on human conjunctival mast cells.

In addition, anti-allergic drugs with a tricyclic skeleton include amelexanox (Amelexanox in Exhibit Ko 1) and nedocromil sodium as well as the present compound and ketotifen (Exhibits Ko 1, 11, 19, and 31, and the entire import of the oral argument). In this regard, amelexanox has a significant inhibitory effect on histamine release from the conjunctiva in guinea pigs (Exhibit Ko 1). However, the present compound does not show a significant effect (Exhibit Ko 1). Further, nedocromil sodium hardly stabilized human conjunctival mast cells in the experiment on cell populations in which human conjunctival mast cells were cultured (Table 1 of the present description). However, the present compound showed a significant stabilizing action on human conjunctival mast cells in the same experiment. In view of the above, only the fact that the compounds are common to the extent that they are tricyclic compounds does not provide a basis for a person ordinarily skilled in the art to expect the same kind and the same level of efficacy in stabilizing human conjunctival mast cells.

Furthermore, ketotifen has been used in various experiments for comparison with the present compound (or the compound of its generic concept) (Exhibits Ko 208 to 210, note that Exhibit Ko 210 is a document after the priority date of the present

case). In Exhibit Ko 1, ketotifen and the present compounds are listed together. However, the ring structure and substituents are different between ketotifen and the present compounds. Therefore, simply because the present compound is used in comparison or listed together with ketotifen as mentioned above, it cannot be deemed that a person ordinarily skilled in the art would have expected that the present compound would have the same kind and the same level of inhibitory effect on histamine release on the basis of the inhibitory effect of ketotifen on histamine release.

The Plaintiff asserts that it would have been possible to deduce the degree of effects of KW-4679 (the present compound) from the degree of effects of ketotifen, since ketotifen is common to the present compound in terms of an anti-allergic drug having a tricyclic skeleton, and ketotifen has been compared in terms of the effects of the generic concept compounds of the present compound and KW-4679, etc. (Exhibits Ko 208 to 210). However, the assertion by the Plaintiff is not acceptable.

Therefore, it cannot be deemed that a person ordinarily skilled in the art, who had read the disclosure of Exhibit Ko 1, could have predicted from the effect of ketotifen that the present compound would have the effect on human conjunctival mast cells as mentioned in the above A.

(C) Further, based on the fact that there were documents of Exhibits Ko 20, 34, and 37 at the time of the priority date of the present case, it will be determined whether or not the stabilizing effect of the present compound on human conjunctival mast cells could have been predicted from these documents.

a. Exhibit Ko 20 discloses that in an experiment of administration of procaterol hydrochloride eye drop solution to the eyeballs of patients with cedar pollen allergy, average inhibition rates of histamine release 5 minutes after the induction were 81.7% for 0.003% eye drop solution, 81.6% for 0.001% eye drop solution, and 79.0% for 0.0003% eye drop solution, and average inhibition rates of histamine release 10 minutes after the induction were 90.7% for 0.003% eye drop solution, 89.5% for 0.001% eye drop solution, and 82.5% for 0.0003% eye drop solution.

In addition, Exhibit Ko 34 discloses that in an experiment of administration of DSCG (disodium cromoglycate) 2% eye drop solution to the eyeballs of patients with cedar pollen allergy, average inhibition rates of histamine release 5 minutes after the induction and 10 minutes after the induction were 73.8% and 67.5%, respectively.

Further, Exhibit Ko 37 discloses that in an experiment of administration of pemirolast potassium eye drop solution to the eyeballs of patients with cedar pollen allergy, average inhibition rates of histamine release 5 minutes after the induction

were 71.8% for 0.25% eye drop solution and 69.6% for 0.1% eye drop solution, and average inhibition rates of histamine release 10 minutes after the induction were 61.3% for 0.25% eye drop solution and 69% for 0.1% eye drop solution.

b. However, the chemical structure of the present compound is remarkably different from those of procaterol hydrochloride (Exhibit Ko 20), disodium cromoglycate (Exhibit Ko 34), and pemirolast potassium (Exhibit Ko 37). In addition, as mentioned in the above (B)b, the present compound and amelexanox, both of which have a tricyclic skeleton, differ in inhibitory effect on histamine release from the conjunctiva in guinea pigs. Further, nedocromil sodium and the present compound have different stabilizing effects on human conjunctival mast cells. Thus, it could have been known to a person ordinarily skilled in the art that the stabilizing effect on human conjunctival mast cells also varies depending on chemical structure of the compound. Therefore, it cannot be deemed that, based on the results of the experiments mentioned in the above a, a person ordinarily skilled in the art could have predicted the stabilizing effect of the present compound on human conjunctival mast cells to be of the same degree as those of the compounds mentioned in the above a.

In addition, from each disclosure of the above a, it cannot be acknowledged that it is clear whether or not procaterol hydrochloride (Exhibit Ko 20), disodium cromoglycate (Exhibit Ko 34), and pemirolast potassium (Exhibit Ko 37) have concentration-dependent effects between 30 μM and 2000 μM on the inhibition rate of histamine release from human conjunctival mast cells. Further, there are no other evidences that it is clear whether or not these drugs have a concentration-dependent effect on the inhibition rate of histamine release from human conjunctival mast cells between 30 μM and 2000 μM.

Therefore, from each disclosure of the above a, it cannot be deemed that it would have been possible to predict that the present compound would have the effect as mentioned in the above A on inhibiting histamine release from human conjunctival mast cells.

C. The Plaintiff asserts that in order for a remarkable effect of Present Invention 1 to be acknowledged, the present compound must have a remarkable effect on inhibition rates of histamine release over the entire range of concentrations from 0.0001 to 5 w/v% and over the entire range of inhibition rates of histamine release from 29.6% to 92.6% as stated in Table 1 of the present description.

However, the effect of Present Invention 1 lies in the fact that the inhibition rate of histamine release increases in a concentration-dependent manner between 30 μM and 2000 μM, reaching a maximum value of 92.6%, and that between these

concentrations, a phenomenon of decreasing the inhibition rate does not occur with higher doses (concentrations) than the dose (concentration) at which the maximum inhibition rate was reached. Thus, it is not required that the present compound exceed the inhibition rates of histamine release of other drugs over the entire range of concentrations from 0.0001 to 5 w/v% and over the entire range of inhibition rates of histamine release of 29.6% to 92.6% as stated in Table 1 of the present description.

Therefore, the above assertion by the Plaintiff is not acceptable.

D. According to the above, it can be acknowledged that the effect of Present Invention 1 is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention. Therefore, it cannot be acknowledged that Present Invention 1 could have been easily made by a person ordinarily skilled in the art.

(6) Present Invention 2

Present Invention 2 is limited to the Z form (cis isomer) of the present compound of Present Invention 1. Further, in Present Invention 2, the matter "inhibits histamine release from a human conjunctival mast cell by 66.7% or more" for defining the invention is added to Present Invention 1. Then, Present Invention 2 achieves the same effect as Present Invention 1. With regard to Present Invention 2, according to the above (5), it can be deemed that the effect of Present Invention 2 is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted from Exhibits Ko 1 and 4, and the common general technical knowledge at the time of the priority date of the present case.

Further, it cannot be acknowledged that a person ordinarily skilled in the art could have predicted the effects of the present compound on the basis of the effect of ketotifen and Exhibits Ko 20, 34, and 37, as mentioned in the above (1).

Therefore, it cannot be acknowledged that Present Invention 2 could have been easily made by a person ordinarily skilled in the art.

(7) According to the above, Reason 1 for Rescission is unfounded.

3. Reason 2 for Rescission (Reason 3 for Invalidation: Erroneous Determinations of Inventive Step Based on Invention of Exhibit Ko 3)

(1) Invention of Exhibit Ko 3

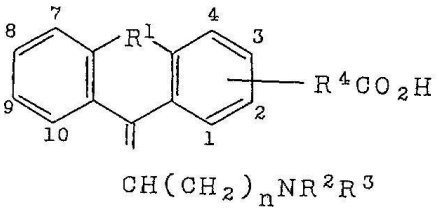
Exhibit Ko 3 discloses as follows.

A. Title of the Invention

TRICYCLIC AROMATIC COMPOUND, METHOD FOR PRODUCING THE SAME, AND PHARMACEUTICAL COMPOSITION

B. Scope of Claims

(1) A compound of formula (I)



(I)

(wherein: R^1 is $-CH_2-CH_2-$, $-CH_2-O-$, or $-O-CH_2-$; R^2 and R^3 are the same or different and are each hydrogen, or a C_{1-4} alkyl, or taken together with the nitrogen atom comprise a nitrogen-containing heterocyclic ring having four to six ring members; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and is bonded to the aromatic ring system at the 2-, 3-, 8-, or 9- position; and n is 0 to 3), or a salt, ester, or amide thereof.

C. Detailed Description of the Invention

(A) The compound of the present invention having anti-allergic activity may be used for the same indications as clinically used antiasthmatic compounds, ... to help control bronchoconstriction or bronchospasm characteristic ... . The present compound is believed to inhibit the release of autacoids (i.e. histamine, serotonin, and the like) from mast cells and to inhibit directly the antigen-induced production of histamine. Thus, they may be classified as mast cell stabilizers with antihistaminic effect.

The compound of the present invention having antihistaminic activity may be used for the same indications as clinically used antihistamines; namely, to relieve detrimental symptoms (caused by histamine release) of nasal stuffiness due to colds and vasomotor rhinitis and for the symptomatic control of allergic conditions including nasal allergy, perennial rhinitis, urticaria, angioneurotic edema, allergic conjunctivitis, food allergy, drug and serum reactions, insect bites and stings, and desensitizing reactions.

(Page 6, left upper column, line 18 to the same page, right upper column, line 19)

(B) The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic, or parenteral (including subcutaneous, intramuscular and intravenous) administration.

(Page 7, left upper column, lines 7 to 9.)

(C) Example 1

(E)/(Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-

carboxylic acid

a) ...

b) ...

c) (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 1)

(Page 7, right lower column, line 13 to page 8, left lower column, line 12)

(D) Example 7

Antihistamine Activity

A. ...B. In vivo Antihistaminic Activity: Guinea pigs (Hartley, male, 300 to 350 g) were fasted for 20 hours and then dosed orally or intravenously with the test compound. One hour after dosing, on an individual basis, the guinea pigs were placed in a clear plastic chamber which was saturated and continually gassed with 0.25% histamine from an aerosol nebulizer. The guinea pigs were monitored for signs of histamine anaphylaxis (e.g. cough, sneeze, strong abdominal movements, cyanoses, or loss of righting). Under the test conditions, control animals collapsed on average within 33 seconds. ED_{50} for protection against histamine were calculated by Probit analysis. In this test, the ED_{50} indicates that at that particular dose 50% of the animals were completely protected against histamine challenge within the time of testing (1 hour post-dosing). Complete protection was defined as no histamine symptoms for six minutes in the aerosol chamber (approximately 10X the collapse time of the control animals).

Table II

Table II

Results of In Vivo Antihistamine Assays

Compound [a]	ED_{50}^{b} (mg/kg, oral) 4hr post dosing
Doxepin (E : Z = 4 : 1)	$\gg 9$
Z - 2 - CO_2H (1)	0.15

a. The purity of these compounds was 96% or more.

b. The number of animals was at least 40.

In addition to these results, it was found that Compound 1 could provide antihistamic activity of very long duration.

(Page 15, left lower column, line 2 to page 16, right upper column, line 10 from the bottom)

(E) Example G

Anaphylactoid Activity

Non-fasted, Wister rats (180 to 300g) were dosed with the test compound (intraperitoneal or oral) 2 hours before compound 48/80 challenge. One hour prior to challenge, 5 mg/kg of propranolol was administered intraperitoneally. The anaphylactoid inducing agent, compound 48/80, which is well known in the art of pharmacology, was given intravenously at 2 mg/kg and the animals were monitored for symptoms of respiratory distress. Data were analyzed by Probit determinations. The response was quantitated by determining the dose of test compound which protected 50% of the animals from death at a given time point.

The above experimental design does not give positive results for selective antihistamines. Also, rats do not respond to histamine (intravenous) with symptoms of anaphylaxis. Agents which block the effects of compound 48/80 are commonly classified as inhibitors of anaphylactic mediators or inhibitors of the release of anaphylactic mediators.

Table III

Table III

Inhibition of Compound 48/80 Induced Anaphylactoid Reaction

Compound	ED_{50} [a,b]
Triprolidine	> 30
Doxepin	0.15
Z - 2 - CO_2H	1.1

a. Dose of compound (oral) providing 50% protection against death induced by compound 48/80.

b. At least 50 animals were used in each assay.

Compound 1 (Example 1) had an LD_{50} in rats of approximately 210 mg/kg (intraperitoneal) and 500 mg/kg or more (oral).

(Page 16, right upper column, line 9 from the bottom to page 16, right lower column,

line 7)

(F) Example 8

Formulations

The active compound is (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid; i.e., Compound 1.

...

(I) - Ophthalmic Solution

Ingredient	Amount per 100.0 ml
Active Compound	0.1 g
Sodium Chloride	0.8 g
Preservative	0.5 g
Water for Injection	q.s. Total Amount 100.0 ml

This formulation is prepared in a similar way to the nasal spray.

(Page 16, right lower column, line 8 to page 18, left upper column, line 13)

(2) Present Invention 1

A. There is no dispute between the parties that the common feature and the different features between Present Invention 1 and Invention of Exhibit Ko 3 are as mentioned in the above No. 2, 4(3)A.

B. It will be determined whether or not a person ordinarily skilled in the art would have been motivated to conceive of the configuration of Present Invention 1 concerning Different Feature 5.

As mentioned in the above 2(2)B(C) to (F), it can be acknowledged that Exhibit Ko 4 discloses that "Compound No. 20 (the present compound)" has the same or slightly superior anti-allergic action to "Compound No. 3 (the compound disclosed in Examples of Exhibit Ko 3)".

The compound represented by the formula (I) in Exhibit Ko 3 is a generic concept of the present compound (11-(3-dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid). Exhibit Ko 3 discloses that "The present compound is believed to inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and to inhibit directly the antigen-induced production of histamine" (the above (1)C(A)). In addition, Exhibit Ko 3 discloses an in vivo experiment of an antihistaminic action of (E)/(Z) 11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid in guinea pigs (Example 7) and a test of an anaphylactoid activity in rats (Example G) (the above (1)C(D), (E)). Further, Exhibit Ko 3 discloses formulation examples including an ophthalmic solution (the above (1)C(F)).

However, the present compound is not disclosed explicitly in Exhibit Ko 3, nor there is any suggestion to select the present compound from the compounds represented by formula (I).

In addition, Example 7 of Exhibit Ko 3 is an experiment of antihistaminic action, and Example G of Exhibit Ko 3 is an experiment in which a drug which blocks an effect of compound 48/80, which is an anaphylactoid activity inducer, was administered to rats receiving compound 48/80. However, Exhibit Ko 3 does not show experimental results supporting that the compound actually inhibited the release of autacoids from mast cells or stabilized human conjunctival mast cells.

On the other hand, in Exhibit Ko 4, in order to test an anti-allergic activity, PCA (passive cutaneous anaphylaxis) test using rats was performed (the above 2(2)B(E), (F)). In addition, Exhibit Ko 4 discloses (in the above 2(2)B(F)) that "The PCA inhibitory action is considered to be based on an action inhibiting release of a chemical mediator such as histamine from skin mast cell." However, these disclosures relate to rat skin mast cells which in animal species and tissue are different from human conjunctival mast cells. Moreover, it is merely an assumption that the release of histamine, etc. from rat skin mast cells can be inhibited. In Exhibit Ko 4, there are no experimental results supporting the fact that the release of histamine was actually inhibited.

Thus, even if Exhibit Ko 4 discloses that "Compound No. 20" (the present compound) has the same or slightly superior anti-allergic action to "Compound No. 3" (the compound disclosed in the Example of Exhibit Ko 3), it cannot be acknowledged that a person ordinarily skilled in the art at the time of the priority date of the present case would have been motivated to derive Compound 20 in Exhibit Ko 4 from the generic concept compounds disclosed in Exhibit Ko 3 and at the same time to use this compound as "a human conjunctival mast cell stabilizing agent" which is not explicitly disclosed in Exhibits Ko 3 and 4. Further, this does not change in light of the disclosure of Exhibit Ko 1.

C. As mentioned in the above 2, it can be acknowledged that the effect of the present compound on human conjunctival mast cells is remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention.

D. Therefore, it cannot be acknowledged that Present Invention 1 could have been easily made by a person ordinarily skilled in the art on the basis of Exhibit Ko 3.

(3) Present Invention 2

A. There is no dispute between the parties that the common feature and the

different features between Present Invention 2 and Invention of Exhibit Ko 3 are the following [i] and [ii] in addition to Different Features 6 and 7 as mentioned in the above (2)A: [i] in Present Invention 2, the oxepin derivative is limited to the Z form (cis isomer) of the present compound, whereas in Invention of Exhibit Ko 3, the oxepin derivative is expressed in a generic concept that includes the present compound, and in Examples of Invention of Exhibit Ko 3, "11-(3-dimethylaminopropylidene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid" is exemplified; and [ii] Present Invention 2 is specified as inhibiting histamine release from human conjunctival mast cells by 66.7% or more, whereas Invention of Exhibit Ko 3 is not specified as such.

B. Present Invention 2 is limited to the Z form (cis isomer) of the present compound of Present Invention 1. Further, in Present Invention 2, the matter "inhibits histamine release from a human conjunctival mast cell by 66.7% or more" for defining the invention is added to Present Invention 1. Then, Present Invention 2 achieves the same effect as Present Invention 1. As mentioned in the above (2)B, it cannot be acknowledged that a person ordinarily skilled in the art at the time of the priority date of the present case would have been motivated to derive Compound 20 in Exhibit Ko 4 from the generic concept compounds described in Exhibit Ko 3 and at the same time to use this compound as "a human conjunctival mast cell stabilizing agent" which is not explicitly disclosed in Exhibits Ko 3 and 4. Further, it can be deemed that the effect of Present Invention 2 is also remarkable beyond the scope of effects that a person ordinarily skilled in the art could have predicted as being achieved by the configuration of the invention. Therefore, it cannot be acknowledged that Present Invention 2 could have been easily made by a person ordinarily skilled in the art.

(4) According to the above, Reason 2 for Rescission is unfounded.

4. Conclusion

In view of the foregoing, the Plaintiff's claim is unfounded. Therefore, the Plaintiff's claim shall be dismissed and the judgment is rendered as mentioned in the main text.

Intellectual Property High Court, Second Division

Presiding Judge MORI Yoshiyuki

Judge MANABE Mihoko

Judge SANO Shin