In case of indicating the suit against trial decision made by the JPO, patent, and case judgment

Patent Right	Date	September 4, 2018	Court	Intellectual Property High Court, First Division
	Case number	2017(Gyo-Ke) 10172		

- A case in which, with regard to a patent according to an invention titled "ANTIVIRAL AGENT," since the compounds according to the respective inventions of the present case cannot be recognized within the range that a person ordinarily skilled in the art could solve the problems of the respective inventions of the present case for newly providing a pharmaceutical composition comprising a compound having an integrase inhibitory action, the statement of each claim in the scope of claims of the respective inventions of the present case cannot be said to conform to the support requirements.

Case type: Rescission of Trial Decision of Invalidation

Result: Dismissed

References: Article 36, paragraph (6), item (i) of the Patent Act

Number of related rights, etc.: Patent No. 5207392, Invalidation Trial No. 2015-800226

Summary of the Judgment

1. The case is a lawsuit for rescission of a trial decision which invalidated the plaintiff's patent concerning the invention titled "ANTIVIRAL AGENT." Each claim in the scope of claims of the present case states that "A pharmaceutical composition provided as an integrase inhibitor, the composition comprising a compound represented by formula (I) ... as an effective ingredient." The trial decision invalidated the patent for violation of enablement requirement and violation of support requirement.

2. For the support requirements, the judgment is stated as follows and concludes no error in the judgment of trial decision.

The problem of each of the present inventions is to newly provide a pharmaceutical composition comprising a compound having an integrase inhibitory action.

However, the present description states no pharmacological data showing that the compound according to each of the inventions of the present case has an integrase inhibitory activity. Moreover, there is no statement about the mechanism by which the compound of each of the inventions of the present case leads to an integrase inhibitory activity.

Furthermore, in the light of the common general technical knowledge at the date of the original filing date in which, due to slight change in modifications to the structure of the integrase inhibitor, a large difference may be caused in its integrase inhibitory action, a person ordinarily skilled in the art could not recognize that the compound according to

each invention of the present case has an integrase inhibitory action from the pharmacological data showing that 27 compounds stated in the test examples of the present description have integrase inhibitory actions.

Furthermore, in light of the common general technical knowledge that molecules having a structure that can serve as a chelate ligand at the time of the original filing date do not necessarily have an integrase inhibitory action, a person ordinarily skilled in the art could not recognize that the compounds according to the present invention of the present case each have an integrase inhibitory action as the compounds according to the present invention of the present case each have a structure that can serve as a chelating ligand.

Besides these issues, there was no common general technical knowledge at the date of the original filing date, which could be recognized by a person ordinarily skilled in the art as the compounds according to the present invention of the present case have an integrase inhibitory action.

Therefore, the compounds according to the respective inventions of the present case cannot be recognized within the range that a person ordinarily skilled in the art could solve the problems of the respective inventions of the present case for newly providing a pharmaceutical composition comprising a compound having an integrase inhibitory action.

Judgment rendered on September 4, 2018
2017 (Gyo-Ke) 10172 The case of seeking rescission of Trial Decision
Date of conclusion of oral argument: July 10, 2018

Judgment

Plaintiff: SHIONOGI & CO., Ltd.

Defendant: MSD K.K.

Main text

Plaintiff's claim shall be dismissed.

The court costs shall be borne by Plaintiff.

Facts and reasons

No. 1 Claim

A trial decision for Invalidation Trial No. 2015-800226 that the JPO made on August 8, 2017 shall be rescinded.

No. 2 Outline of the case

1 Outline of procedures, etc. at the JPO

(1) Plaintiff filed a patent application titled "Antivirus agent" on March 11, 2009 (a divisional application of Japanese Patent Application No. 2003-521202 filed on August 8, 2002), and registered it as a patent on March 1, 2013 (Patent No. 5207392). (Number of claims: 3. Exhibit Ko 116. Hereinafter this patent is referred to as "the Patent".)

(2) Defendant requested a trial for patent invalidation with respect to the Patent on December 17, 2015, which was assigned to a collegial body as a case of Invalidation Trial No. 2015-800226 (Ko 97).

(3) Plaintiff requested for correction on April 13, 2017 to the effect that the scope of the claims of the Patent shall be corrected (hereinafter referred to as "the Correction"; Exhibit Ko 112).

(4) JPO affirmed the Correction on August 8, 2017, and made a decision as per the attached appendix (copy) to the effect that the Patent should be invalidated (hereinafter referred to as "the trial decision") and its certified copies were served for Plaintiff on August 17.

(5) Plaintiff filed a suit for the case seeking for the rescission of the trial decision on September 8, 2017.

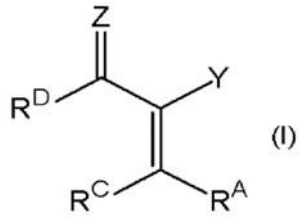
2 The recitation of the Claims

The recitation of Claims 1 to 3 of the scope of the claims after the Correction is set forth as below (Exhibit Ko 116, 112). Hereinafter, each of the claimed inventions is referred to as "invention 1," etc., and the respective inventions are collectively referred to as "each of the Inventions." Further, the specification (Exhibit Ko 116) is referred to as "the specification."

[Claim 1]

A pharmaceutical composition of integrase inhibitor, the composition comprising as an active ingredient a compound represented by the following formula (I):

[Chemical Formula 1]

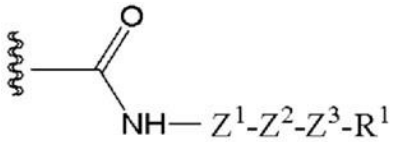


(I)

(where

R^A is a compound represented by the formula:

[Chemical Formula 3]



(where the group represented by the formula: -Z^1-Z^2-Z^3-R^1 is 4-fluorobenzyl); Y is hydroxy;

Z is an oxygen atom;

R^C and R^D together form a 5-membered or 6-membered ring that may contain a heteroatom together with adjacent carbon atoms, and the ring may be a condensed ring with a benzene ring;

the ring formed by R^C and R^D may be substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (where each Z^1 and Z^3 is, independently from each other, a single bond, or linear or branched alkylene with a carbon number of 1 to 6; Z^2 is a single bond, -S-, -SO-, -$NHSO_2$-, -O- or -NHCO-; R^1 is an optionally-substituted phenyl, an optionally-substituted 5 to 8-membered aromatic heterocyclic group, an optionally-substituted cycloalkyl with a carbon number of 3 to 6, or an optionally-substituted heterocycle (each substituent group of "optionally-substituted" is, independently from each other, selected from an alkyl, haloalkyl, halogen, and alkoxy));

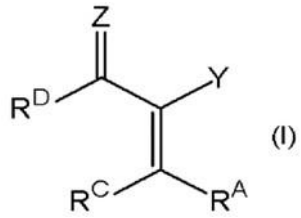
furthermore, the ring formed by R^C and R^D may be substituted with an alkyl at a position adjacent to carbon atom to which =Z is bonding and a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (where Z^1, Z^2, Z^3 and R^1 have the same meanings as above)), or

a pharmaceutically acceptable salt thereof or a solvated form thereof.

[Claim 2]

A pharmaceutical composition of integrase inhibitor, the composition comprising, as an active ingredient, a compound represented by the following formula (I):

[Chemical Formula 1]

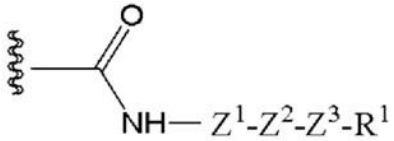


(I)

(where

R^A is a compound represented by the formula:

[Chemical Formula 3]



(where the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ is 4-fluorobenzyl); Y is hydroxy;

Z is an oxygen atom;

R^C and R^D together form a 5-membered or 6-membered ring containing an N atom together with adjacent carbon atoms;

the ring formed by R^C and R^D may be substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (where Z^1 and Z^3 each is, independently from each other, a single bond or linear or branched alkylene with a carbon number of 1 to 6;

Z^2 is a single bond, -S-, -SO-, $-NHSO_2-$, -O-, or -NHCO-; R^1 is an optionally-substituted phenyl, optionally-substituted 5 to 8-membered aromatic heterocyclic group, optionally-substituted cycloalkyl with a carbon number of 3 to 6 or optionally-substituted heterocycle (each substituent group of "optionally-substituted" is, independently from each other, selected from an alkyl, haloalkyl, halogen, and alkoxy));

furthermore, the ring formed by R^C and R^D may be substituted with an alkyl at a position other than a position that is substituted with the group represented by the

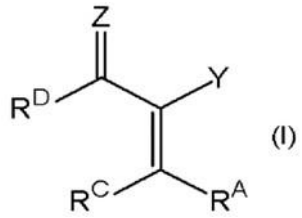
formula: $-Z^1-Z^2-Z^3-R^1$ (where Z^1, Z^2, Z^3 and R^1 have the same meanings as above)); or

a pharmaceutically acceptable salt thereof or a solvated form thereof.

[Claim 3]

A pharmaceutical composition of integrase inhibitor, the composition comprising, as an active ingredient, a compound represented by the following formula (I):

[Chemical Formula 1]

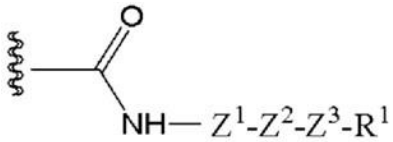


(I)

(where

R^A is a compound represented by the formula:

[Chemical Formula 3]



(where the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ is 4-fluorobenzyl); Y is hydroxy;

Z is an oxygen atom;

R^C and R^D together form a 6-membered ring containing a heteroatom together with adjacent carbon atoms;

the ring formed by R^C and R^D may be substituted at the 3-position given that the carbon atom bonding to =Z is the 1-position with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (where each Z^1 and Z^3 is, independently from each other, a single bond, or a linear or branched alkylene with a carbon number of 1 to 6; Z^2 is a single bond, -S-, -SO-, $-NHSO_2-$, -O-, or -NHCO-; R^1 is optionally-substituted phenyl, optionally-substituted 5 to 8-membered aromatic heterocyclic group, optionally-substituted cycloalkyl with a carbon number of 3 to 6 (each substituent group of "optionally-substituted" is, independently from each other, selected from an alkyl, haloalkyl, halogen, and alkoxy; with the proviso that Z^1, Z^2, and Z^3 are not a single bond simultaneously));

furthermore, the ring formed by R^C and R^D may be substituted with an alkyl at a position adjacent to carbon atom to which =Z is bonding and at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (where Z^1, Z^2, Z^3, and R^1 have the same meanings as above))

(excluding N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide), a pharmaceutically acceptable salt thereof, or a solvated form thereof.

3 Abstract of reasons of trial decision

The reason for trial decision is as per the attached written trial decision (copy) and the attached ruling of correction (copy). In summary, (1) the Detailed Description of the Invention of the specification does not disclose definitely and sufficiently to the extent that allows a person ordinarily skilled in the art to implement each of the Inventions, and thus does not conform to the requirement as provided in Article 36(4) of the Patent Act (hereinafter referred to as "enablement requirement".), and (2) the recitation of the scope of claims according to each of the Inventions does not conform to the requirement as provided in Article 36, paragraph (6), item (i) of the Patent Act (hereinafter referred to as "support requirement") since each of the Inventions is not described in the Detailed Description of the Invention of the specification.

4 Abbreviated names of Compounds

The group represented by [Chemical formula 2] of paragraph [0004] of the specification is abbreviated as "C ring."

The group represented by [Chemical formula 3] of paragraph [0004] of the specification is abbreviated as "X/R^B-containing group."

The group represented by "formula: $-Z^1-Z^2-Z^3-R^1$" of paragraph [0004] of the specification is abbreviated as "Z^{1-3}/R^1-containing group."

Fifteen kinds of compounds of Compound A-7, A-12-a, A-17, A-17-c, A-50, A-141-k, A-158, E-8, E-16, F-4, H-7, I-4, J-4, L-4, and M-6 described in the specification are referred to as "Group A, etc. test example compounds," and twelve kinds of compounds of Compound B-6-a, B-6-d, B-12, B-12-b, B-29, B-68, C-22, C-26, C-39, D-5, G-7, and K-4 are referred to as "Group B, etc. test example compounds."

5 Grounds for rescission

(1) Errors in the determination of the enablement requirement (Grounds 1 for rescission)

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

(omitted)

No. 4 Court decision

1 Grounds 2 for rescission (Errors in the determination of the support

requirement)

(1) Support Requirement

The determination of whether or not the recitation of the Claims might comply with the support requirement should follow the steps of: comparing the recitation of the Claims and the descriptions of the Detailed Description of the invention; and considering whether or not the invention recited in the Claims might fall within the scope in which person ordinarily skilled in the art could recognize that a problem to be solved by the invention might be solved by the description of the Detailed Description of the Invention, or considering whether or not the invention recited in the Claims might fall within the scope in which person ordinarily skilled in the art could recognize without such description or suggestion in view of common technical knowledge as of the filing that the problem to be solved by the invention might be solved.

(2) The recitation of the Claims

The scope of claims according to each of the Invention is as per recited in [Claim 1] and [Claim 3] of the aforesaid No. 2, 2.

(3) The statement of the detailed explanation of the invention of the specification

The specification (Exhibit Ko 116) describes the following matters as an explanation of each of the invention: Note that the specification contains almost 350 pages, in which an explanation is given to the invention of the original application. The Correction does not correct the statement of the detailed explanation of the invention.

A Technical Field ([0001])

Each of the Inventions relates to a pharmaceutical composition to be used as an antivirus agent, in particular an integrase inhibitor.

B Background Art ([0002], [0034])

Human Immunodeficiency Virus (HIV) is known as a cause of acquired immunodeficiency syndrome (AIDS). Reverse transcriptase inhibitors and protease inhibitors are the major therapeutic agents. However, these inhibitors have problems such as side effects of renal disease and the appearance of resistant virus. Thus there is need for the development of anti-HIV drug having an action mechanism different from them. An integrase inhibitor inhibits the action of an integrase, which is produced by a retrovirus such as HIV to grow inside animal cells, thereby preventing the growth of the virus. The prior art documents disclose various compounds as integrase inhibitors. However, as of the filing date of the original application, no integrase inhibitor had been placed on the market.

C Problem to be solved by the invention ([0003])

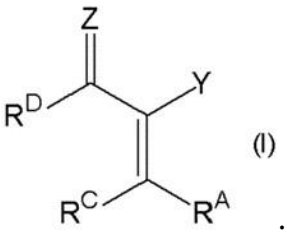
In the aforementioned circumstances, the development of a novel integrase inhibitor is needed.

D Means for solving the problem ([0004], [0005])

The inventors have found a compound as a novel antivirus agent that satisfies each of the following requirements (A) to (H):

(A) The group represented by the formula:

[Chemical Formula 1]



(I)

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(B) R^C and R^D

R^C and R^D together form a ring with adjacent carbon atoms, the ring may be a condensed ring.

(C) Y

hydroxy, mercapto, or amino

(D) Z

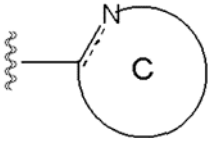
oxygen atom, sulfur atom, or NH

(E) R^A

Formula: Group represented by [Chemical formula 2] or Formula: Group represented by [Chemical formula 3]

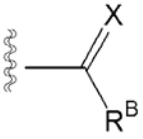
a Formula:

[Chemical Formula 2]



C ring is a nitrogen-containing aromatic heterocycle with at least one atom of atoms adjacent to an atom having a bond being a non-substituted nitrogen atom. A dashed line represents the presence or absence of bonding.

b Formula: [Chemical Formula 3]



X is an oxygen atom, sulfur atom, or NH, and R^B is a substituent selected from

the following substituent group A.

(F) Ring formed by R^C and R^D, C ring, or R^B

At least one of a ring formed by R^C and R^D, C ring, or R^B is substituted with a group represented by the following formula: $-Z^1-Z^2-Z^3-R^1$, and further a ring formed by R^C and R^D, C ring, or R^B may be substituted by a non-interfering substituent group at a position other than a position that is substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$.

(G) Formula: $-Z^1-Z^2-Z^3-R^1$

Z^1 and Z^3 each is, independently from each other, a single bond, optionally-substituted alkylene, or optionally-substituted alkenylene; Z^2 is a single bond, optionally-substituted alkylene or optionally-substituted alkenylene, -CH(OH)-, -S-, -SO-, $-SO_2-$, $-SO_2NR^2-$, $-NR^2SO_2-$, -O-, $-NR^2-$, $-NR^2CO-$, $-CONR^2-$, -C(=O)-O-, -O-C(=O)-, or -CO-; R^2 is hydrogen, an optionally-substituted alkylene, optionally-substituted alkenyl, optionally-substituted aryl, or optionally-substituted heteroaryl; R^1 is an optionally-substituted aryl, optionally-substituted heteroaryl, optionally-substituted cycloalkyl, optionally-substituted cycloalkenyl, or optionally-substituted heterocycle

(H) Substituent group A

Group consisting of hydrogen, halogen, alkoxycarbonyl, carboxy, alkyl, alkoxy, alkoxyalkyl, nitro, hydroxy, alkenyl, alkynyl, alkylsulfonyl, optionally-substituted amino, alkylthio, alkylthioalkyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, optionally-substituted cycloalkyl, optionally-substituted cycloalkenyl, optionally-substituted heterocycle, nitroso, azide, amidino, guanidino, cyano, isocyano, mercapto, optionally-substituted carbamoyl, sulfamoyl, sufoamino, formyl, alkylcarbonyl, alkylcarbonyloxy, hydrazino, morpholino, optionally-substituted aryl, optionally-substituted heteroaryl, optionally-substituted aralkyl, optionally-substituted heteroarylalkyl, optionally-substituted aryloxy, optionally-substituted heteroaryloxy, optionally-substituted arylthio, optionally-substituted heteroarylthio, optionally-substituted aralkyloxy, optionally-substituted heteroarylalkyloxy, optionally-substituted aralkylthio, optionally-substituted heteroarylalkylthio, optionally-substituted aryloxyalkyl, optionally-substituted heteroaryloxyalkyl, optionally-substituted arylthioalkyl, optionally-substituted heteroarylthioalkyl, optionally-substituted arylsulfonyl, optionally-substituted heteroarylsulfonyl, optionally-substituted aralkylsulfonyl, and optionally-substituted heteroarylalkylsulfonyl

E Examples ([0035])

The specification describes production method and physical property data of

synthesized compounds for 33 compounds as Group A compounds and partially substituted compounds thereof, 26 compounds as Group B compounds and partially substituted compounds thereof, 16 compounds as Group C compounds and partially substituted compounds thereof, 2 compounds as Group D compounds and partially substituted compounds thereof, 13 compounds as Group E compounds and partially substituted compounds thereof, 1 compound as Group F compounds and partially substituted compounds thereof, 1 compound as Group G compounds and partially substituted compounds thereof, 2 compounds as Group H compounds and partially substituted compounds thereof, 2 compounds as Group I compounds and partially substituted compounds thereof, 3 compounds as Group J compounds and partially substituted compounds thereof, and 1 compound each as Group K, L, and M compounds. Further, the specification describes an enormous number of compounds as a compound capable of being synthesized similarly to each of the above compounds.

However, the compound corresponding to the structure of the Invention 1 is only Compound C-71 (page 214) among these compounds. Further, compounds corresponding to the structures of the Invention 2 and the Invention 3 are not described in the specification.

F Test example ([0036])

The specification describes compound concentrations (IC_{50}) corresponding to the inhibitory rate of 50% based on enzyme assay for 27 compounds (Group A, etc. test example compounds and Group B, etc. test example compounds) as per the attached test example [Table 1].

On the other hand, the specification fails to show any pharmacological data supporting this, although it discloses that compounds other than the above 27 compounds showed comparable or superior integrase inhibitory activity. There are no pharmacological data showing integrase inhibiting effects for the Compound C-71.

G Effects ([0034], [0037])

The compound according to each of the invention is a novel integrase inhibitor with an integrase inhibitory activity and useful for an anti-HIV drug, etc.

H Mechanism

The specification fails to disclose a mechanism that causes the compound according to each of the inventions to show an integrase inhibitory activity.

(4) Problem of each of the inventions

According to the description of the Detailed Description of the Invention of the specification, the problem to be solved by each of the inventions is to newly provide a pharmaceutical composition comprising a compound having an integrase inhibitory

activity.

(5) Common general knowledge of integrase inhibitor

A Change in modification of the structure of integrase inhibitor

It is a common general knowledge for a person ordinarily skilled in the art that a slight modification of structure in a compound may result in different pharmacological effects (Exhibits Ko 16, 17, 35).

Further, with regard to an integrase inhibitor, Yves Pommier and Nouri Neamati of National Cancer Institute, molecular pharmacology labs "Inhibitor of human immunodeficiency virus integrase" (1999. Ko 52) discloses that "many inhibitors have been identified so far. To our knowledge, however, all of these agents are highly selective for IN (Court's note: Integrase protein), and lack desired properties of showing a strong antivirus activity." (page 442), "A rule of adjacent hydroxyl group may not be applied to all the known IN inhibitors. ... This suggests that the other part of bonding in an inhibitor is a key of the activity and probably, their selectivity." (page 445). In a declaration prepared by Professor Nouri Neamati in 2015 (Ko 53, page 11), it is stated that "By 2001, several specific motifs ... had been recognized as a common constituent component for the success of a lead compound; however, it had been universally understood that a small change in a candidate compound might have a significant effect even on a result of an initial-stage in-vitro assay."

Consequently, it must be said that a person ordinarily skilled in the art had common general knowledge as of the filing date of the original application that a large difference might be produced in an integrase inhibitory activity due to a slight modification to a structure of an integrase inhibitor.

B Relationship between a molecule having a chelate ligand and an integrase inhibitor

(A) In general formula of a compound according to each of the inventions, Y of [Chemical formula 1] is a hydroxy, Z is an oxygen atom, and [Chemical formula 3] also has an oxygen atom. Thus the compound according to each of the inventions has a structure in which a heteroatom (O) capable of donating a lone electron pair to the other atom can be a chelate ligand. As set forth below, however, it is recognized that it was common general knowledge as of the filing date of the original application that a molecule having a structure that could be a chelate ligand did not necessarily have an integrase inhibitory activity.

(B) Specifically, it is recognized that there are two or more ligands containing an atom (O, N, S, P, As, etc.) coordinated with a metal ion in a molecule, and there are many compounds in which a chelating ring coordinating these ligands constitutes a 5-

membered or 6-membered ring (Exhibit Ko 29-2). However, it was obvious that a molecule having a structure that could be a chelate ligand did not necessarily have an integrase inhibitory activity.

Further, "Review: Retrovirus integrase inhibitor, 2000: Current situation and foresight" written by Yves Pommier, Christophe Marchand and Nouri Neamati of National Cancer Institute, molecular pharmacology labs (Exhibit Ko 29-6) discloses that "Chelation of divalent metal cofactor (Mg^{2+} or Mn^{2+}) in an enzymatic catalytic site has been proposed with respect to hydroxylated aromatics (FIG. 4). However, no direct evidence of such possibility has been shown." (page 141). Further, diketo acid derivatives bind to a mononucleotide binding site of integrase, and have only been found to bind with DDE motif (page 141), but it discloses that "a sole class of inhibitor that seems to selectively target integrase is only diketo acids ... ." (page 144). Furthermore, in a drawing for illustrating a binding site of diketo acid integrase inhibitor, the compound has a chelate ligand; however, the relationship with a metal binding site is not at all shown (page 142, FIG. 2). The document does not show that a molecule having a structure that could be a chelate ligand has an integrase inhibitory activity.

Further, the aforesaid Exhibit Ko 52 discloses that "we assume that a large class of inhibitor of HIV-1IN; i.e., hydroxylated aromatics, may function as a metal chelator (FIG 14.3)." (page 435) As aforementioned, it explains that "a rule of adjacent hydroxyl group may not be applied to all the known IN inhibitors. ... This suggests that the other part of bonding in an inhibitor is a key factor of the activity and probably, a key factor of their selectivity." (page 445). "Expert Opinion on Investigational Drugs," written by Nouri Neamati (2001. Exhibit Ko 54) states that "it has been found that a promising class of inhibitor of hydroxylated aromatics (FIG. 2) may potentially be a metal chelator." (page 283), and "hydroxylated aromatics can chelate an Mg^{2+} ion, and probably form a ternary complex with ... an activity moiety residue of integrase." (page 284). Each of these documents only assumes the function of a chelate ligand, and negates the fact that a molecule having a structure that can be a chelate ligand is a sufficient condition for causing the integrase inhibitory activity.

Furthermore, Nouri Neamati and others, "Salicylhydrazine-Containing Inhibitors of HIV-1 Integrase" (1998. Exhibit Ko 29-7) explains that "We propose that HIV-1 integrase catalytic activity and inhibition of DNA bonding are strictly Mn^{2+} dependent, and thus this site may interact with HIV-1 integrase by the chelation of this site with metal in an integrase active site." (page 3202). Also this document only proposes the function of a chelate ligand.

In addition, Plaintiff alleges that WO968 document (Exhibit Ko 29-11, 92) discloses that it is preferable for an integrase inhibitory activity to have a lone electron pair at a specific position. An atom having a lone electron pair is commonly present in a pharmaceutical compound such as an enzyme inhibitor. Its roles are supposed to vary. Thus it cannot be seen that a molecule having a lone electron pair at a specific position is a sufficient condition for causing an integrase inhibitory activity.

Consequently, although a person ordinarily skilled in the art had recognized as of the filing date of the original application that a molecule with a structure that can be a chelate ligand might possibly be involved with an integrase inhibitory activity by any method, he should have had common general knowledge that the molecule with a structure that can be a chelate ligand did not necessarily have an integrase inhibitory activity.

(6) Whether a person ordinarily skilled in the art could recognize that a problem to be solved by each of the invention might be solved

The problem to be solved by each of the invention is to newly provide a pharmaceutical composition comprising a compound having an integrase inhibitory activity.

However, the specification states no pharmacological data showing that the compound according to each of the invention has an integrase inhibitory activity. Moreover, there is no statement about the mechanism that causes the compound according to each of the invention to show an integrase inhibitory activity.

Furthermore, in the light of the aforesaid common general technical knowledge as of the filing date of the original application in which, due to a slight change in a modification to the structure of an integrase inhibitor, a large difference may be caused in its integrase inhibitory activity, a person ordinarily skilled in the art could not recognize from the pharmacological data showing that Group A, etc. test example compounds and Group B, etc. test example compounds had an integrase inhibitory activity that the compound according to each of the invention also had an integrase inhibitory activity.

Furthermore, in light of the aforesaid common general technical knowledge as of the filing date of the original application that a molecule having a structure that can serve as a chelate ligand does not necessarily have an integrase inhibitory activity, a person ordinarily skilled in the art could not recognize that the compound according to each of the inventions has an integrase inhibitory activity as the compound according to each of the inventions has a structure that can serve as a chelate ligand.

Besides these issues, there was no common general technical knowledge as of

the filing date of the original application, which could be recognized by a person ordinarily skilled in the art as stating the compounds according to each of the inventions have an integrase inhibitory activity.

Therefore, the compounds according to each of the inventions cannot be recognized within the range that a person ordinarily skilled in the art could solve the problem to be solved by each of the invention to newly provide a pharmaceutical composition comprising a compound having an integrase inhibitory activity.

(7) Plaintiff's argument

Plaintiff alleges that, in light of the common general knowledge as of the filing date of the original application, a person ordinarily skilled in the art would recognize that the compound described in the specification has a site to be maintained such as a chelate ligand structure, and a site where a modification is permitted, and on the basis of such recognition, recognize from pharmacological data of Group A, etc. test example compounds and Group B, etc. test example compounds described in the specification that the compound according to each of the inventions has an integrase inhibitory activity.

However, the Plaintiff's argument is not acceptable. The reason is set forth as below.

A Integrase inhibitory activity by chelate ligand

(A) Plaintiff alleges that it was demonstrated as of the filing date of the original application that a molecule having a chelate ligand reacted with two metal ions located in an active center of integrase to have an integrase inhibitory activity.

(B) However, Exhibit Ko 29-6 as Plaintiff cites only shows that the possibility of an integrase inhibitory activity caused by the chelation to a metal ion had been suggested, and according to the description that diketo acid derivatives binding to a mononucleotide site of integrase seem to be a sole integrase inhibitor, it had not yet been clarified that a metal binding site is an action site of an integrase inhibitor. Further, as aforementioned, Exhibit Ko 29-7 only suggests the idea that the chelation of a metal ion provides an integrase inhibitory activity. Furthermore, Exhibit Ko 52 and Ko 54 only express an integrase inhibitory activity by chelation of metal ion as the presumption or the possibility with a reservation.

(C) In addition, Exhibit Ko 52 discloses that "it is suggested that IN inhibition necessitates at least two hydroxyl groups that are spatially adjacent to each other, but are not always at an ortho position in a same ring." "One possible action mechanism for these types of compounds is to block a polynucleotide bonding and a catalytic site of IN ... . However, it does not eliminate the possibility of a phenolic hydroxyl group

being possibly served as a hydrogen bond donor." (page 446), and the document suggests that the positional relationship of hydroxyl groups having a heteroatom and its action mechanism in an integrase inhibitor could not be sufficiently identified.

(D) Further, WO968 document (Exhibit Ko 29-11, 92. page 12, page 16) discloses that "At a position of heteroatom constituting heteroaryl, oxygen atom, and nitrogen atom are located respectively, and it is preferable to show a high integrase inhibitory activity." "it is preferable that the heteroatom has a lone electron pair that is not involved with a conjugation of an aromatic ring." However, the document does not explain the fact that a compound having an integrase inhibitory activity has a lone electron pair at a specific position in connection with the fact that the lone electron pair has an integrase inhibitory activity caused by the chelation to a metal ion.

(E) Consequently, even if it were known that integrase had two metal ions at an active center and a chelate ligand bound to a metal ion, it should have been a matter for speculation as of the filing date of the original application that a molecule having a structure that could be a chelate ligand reacted with two metal ions that were located at an active center of integrase to have an integrase inhibitory activity.

Therefore, a person ordinarily skilled in the art could not have understood that a site to be maintained for causing an integrase inhibitory activity in the compounds described in the specification as an integrase inhibitor was the chelate ligand structure, etc. and the remaining site was allowed to be modified.

B Description of Prior Art Documents

(A) Plaintiff alleges that the prior art documents represent the chelate ligand structures in a general formula of a compound having an integrase inhibitory activity, and thus it would be recognized by the comparison of the description of the prior art documents that the chelate ligand structure is a feature of a compound described in the specification.

(B) First, as aforementioned, however, even if a test compound is limited to ones with two or more coordinating groups containing an atom that coordinates a metal ion and a chelate ring with these coordinating groups being coordinated constitutes a 5-membered ring and a 6-membered ring, a large number of such compounds are present. Further, a compound with such a structure is very common. Thus it cannot be directly concluded as a feature of the compound that the compound has three groups containing a heteroatom such as an oxygen atom and a nitrogen atom, and the heteroatoms are placed at a specific distance. Further, the prior art document does not at all describe a mechanism that causes a compound having the chelate ligand structure to show an integrase inhibitory activity.

(C) Further, not all the compounds described as a compound having an integrase inhibitory activity in 11 prior art documents described in [Background Art] of the specification have a chelate ligand structure.

Specifically, WO968 document (Exhibit Ko 29-11, 92) describes a general formula of a compound having an integrase inhibitory activity in Claim 1 of the scope of the claims. Z of formula (I) is defined as "hydrogen, an optionally-substituted alkyl, or optionally-substituted aralkyl," which does not necessarily have a heteroatom. Thus it cannot be recognized from WO968 document that the chelate ligand structure is essential for integrase inhibitory activity.

WO245 document (Exhibit Ko 29-8, 89) discloses a compound having an integrase inhibitory activity. Y of formula (I) in Claim 1 of the scope of the claims is defined as "COOR (R is hydrogen or ester residue), optionally-substituted aryl, or optionally-substituted heteroaryl.", which does not necessarily have a heteroatom. Further, the heteroatoms in a compound of Example 96 (oxygen atom in -OH, oxygen atom in $-CO_2H$) are positioned at a distance of 5 or 6 times as long as interatomic bonding, and are different from the chelate ligand structure. Thus it cannot be recognized from WO245 document that the chelate ligand structure is essential for integrase inhibitory activity.

WO086 document (Exhibit Ko 29-10, 88) describes a general formula of a compound having an integrase inhibitory activity in Claim 1 of the scope of the claims. Y of formula (I) is defined as "$COOR^A$ (R^A is hydrogen or ester residue), $CONR^BR^C$ (R^B and R^C are, independently from each other, hydrogen or amide residue), optionally-substituted aryl, optionally-substituted heteroaryl," which does not necessarily have a heteroatom. Thus it cannot be recognized from WO086 document that the chelate ligand structure is essential for integrase inhibitory activity.

Consequently, it can only be seen from the description of the prior art documents that certain compounds having an integrase inhibitory activity from the prior art documents have a chelate ligand structure.

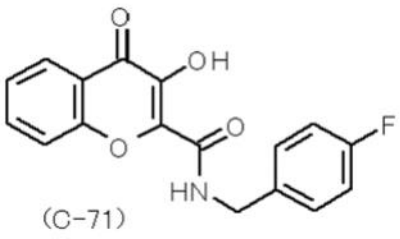
(D) Therefore, a person ordinarily skilled in the art could not have understood that a site to be maintained for causing an integrase inhibitory activity in the compounds described in the specification as an integrase inhibitor was the chelate ligand structure, etc. and the remaining site was allowed to be modified.

C Bioisostere

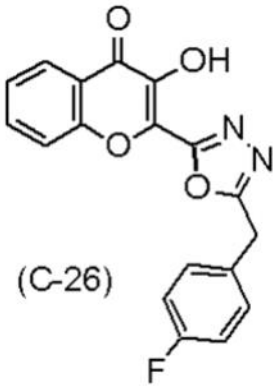
Plaintiff alleges that a compound with an amide (-NHCO-) and 1,3,4-oxadiazole derived divalent connective groups are bioisosteres, and thus it can be seen that the compounds according to each of the inventions also have an integrase inhibitory

activity, similar to Compound C-26 whose pharmacological data of integrase inhibitory activity were shown in the specification.

A compound corresponding to the structure of Invention 1 is only Compound C-71 among the compounds described in the specification. Further, if the structural formula of Compound C-71 and Compound C-26 whose pharmacological data are shown are compared as in the following (the specification, page 200, 214), and the structural formulas differ from each other only in amide (-NHCO-) and 1,3,4-oxadiazole-derived divalent connective groups.



(C-71)



(C-26)

However, Exhibit Ko 93 only discloses that "heterocyclic rings of 1,2,4-oxadiazole (92), 1,3,4-oxadiazole (93), and 1,2,4-triazole (94) are also used as a substitute of amide or ester bond." (page 3170). It does not suggest that, even if the former were a substitute of the latter, the latter is a substitute of the former. Further, first of all, it cannot be said that the compounds obtained by the substitution with bioisosteres always show biological activity comparable to that of an original pharmaceutical (Exhibit Ko 93, page 3165).

Consequently, it cannot be said that the substitution of divalent connective group derived from 1,3,4-oxadiazole in Compound C-26 with amide shows a comparable biological activity. Therefore, even if a compound according to Invention 1 of Compound C-71 was only the one in which a connective group is substituted with amide in comparison to Compound C-26, which was demonstrated to have an integrase inhibitory activity by enzyme assay in the specification, it cannot be seen that Compound C-71 has an integrase inhibitory activity, similarly to Compound C-26.

D Additional test results

Plaintiff alleges that it has been demonstrated by an additional test that the compound according to each of the inventions has an integrase inhibitory activity.

However, as aforementioned, the specification fails to describe pharmacological

data showing that the compound according to each of the inventions has an integrase inhibitory activity, nor does it include statement about the mechanism that causes the compound according to each of the inventions to show an integrase inhibitory activity. In the light of the common general technical knowledge as of the filing date of the original application, a person ordinarily skilled in the art could not recognize from the matters described in the specification that the compound according to each of the inventions has an integrase inhibitory activity. Regardless of the fact that the disclosure of the specification is to such an extent as described above, it is impossible to use the results of an experiment that has been made after the filing date of the original application to support the technical idea in order to clarify the fact that a technical idea that the compound according to each of the inventions has an integrase inhibitory activity was not a simple speculation of the inventor as of the filing date of the original application.

Therefore, it cannot be seen from the additional test results of the compound according to each of the inventions that the recitation of the scope of the claims according to each of the invention conforms to the support requirement.

E Drug Design

Plaintiff alleges that the understanding of a site to be maintained being a chelate ligand structure in a compound described in the specification coincides with the idea of drug design through a technique of overlapping compounds.

However, it is a matter of common general knowledge for a person ordinarily skilled in the art that a slight modification of structure in a compound may result in different pharmacological effects, which is similar to the case of integrase inhibitor. Consequently, the overlapping of compounds described in the specification and prior art documents is not sufficient to find that it is a chelate ligand structure that causes integrase inhibitory activity in these compounds.

F Fluorobenzyl group

Plaintiff alleges that a person ordinarily skilled in the art would recognize the importance of a fluorobenzyl group in a compound described in the specification and recognize that the fluorobenzyl group is a site to be maintained to perform an integrase inhibitory activity.

However, before the filing date of the original application, there is no document to specifically explain a mechanism that causes a compound having a fluorobenzyl group to show an integrase inhibitory activity. Further, in a general formula of a compound disclosed in the invention of the original application as having an integrase inhibitory activity, it is not essential to bind a fluorobenzyl group to X/R^B-containing

group or an end of C ring. The compound according to each of the inventions has a fluorobenzyl group, but this was not an essential structure in the claims before the Correction. The specification describes Group A, etc. test example compounds and Group B, etc. test example compounds as compounds in which an integrase inhibitory activity was confirmed by enzyme assay; however, these compounds include a compound without a fluorobenzyl group (Compound B-6-a, B-6-d, B-12).

Consequently, a person ordinarily skilled in the art could not understand that a fluorobenzyl group is a site to be maintained in a compound described in the specification to cause integrase inhibitory activity.

G Back side ring (R^C/R^D ring)

Plaintiff alleges that a back side ring (R^C/R^D ring) supporting a chelate ligand structure is important to cause an integrase inhibitory activity.

However, before the filing date of the original application, there was no document to explain that the presence of a back side ring supports the chelate ligand structure, and thereby causing the compound having the structure to show an integrase inhibitory activity. Further, the specification (page 59) discloses that a back side ring (R^C/R^D ring) "may be substituted by a non-interfering substituent group. ... The non-interfering substituent group means a substituent group that does not interfere with an integrase inhibitory activity." It explains that a back side ring is sufficient as long as it does not interfere with an integrase inhibitory activity. There is no positive meaning to support the chelate ligand structure with respect to the function of the back side ring from the description of the specification.

Consequently, a person ordinarily skilled in the art could not understand that a back side ring (R^C/R^D ring) supporting the chelate ligand structure is important in a compound described in the specification to cause an integrase inhibitory activity.

H Similarity between individual compounds described in the specification and those described in the prior art documents

Plaintiff alleges that the individual compounds described in the specification and the prior art documents as having an integrase inhibitory activity have similarities in that they have a chelate ligand structure.

First, the test example of the specification describes an integrase inhibitory activity of a compound where X/R^B-containing group is not amino group, but "aryl or heteroaryl" (Compound A-7, A-12-a, A-17, A-17-c, A-50, A-158, E-8, F-4, H-7, I-4, J-4, L-4, M-6) in a general formula of a compound according to each of the inventions and a compound where R^A is a C-ring (Compound B-29, C-26, D-5, G-7, K-4) by enzyme assay. However, it is a common general knowledge for a person ordinarily

skilled in the art that a slight modification of structure in a compound may result in different pharmacological effects, which is similar to the case of integrase inhibitor. It cannot be recognized that a site not in common does not affect an integrase inhibitory activity, focusing on a site common to these compounds.

Further, many compounds described together with pharmacological data as having an integrase inhibitory activity in the prior art documents may be categorized from various viewpoints, and a structure common to compounds respectively categorized may be variously extracted. For example, in the specification ([0002]), the compounds described in the prior art documents are classified into 1,3-dioxobutanoic acids, 1,3-propanediones etc., acrylic acid derivatives, aza or polyazanaphthalenylcarboxamide derivatives, etc. In addition, similarly to the above, it cannot be recognized that a site not in common does not affect an integrase inhibitory activity, focusing on a site common to the aforesaid compounds described in the prior art documents.

In addition, even if a comparison should be made between individual compounds selected from many compounds described in the specification and the prior art documents and analyzed that the chelate ligand structures had in common, a criterion for selecting individual compounds for comparison is first of all indefinite unless it is premised on the chelate ligand structure. Further, it is also indefinite as to how a site other than the chelate ligand structure in common sites and or a non-common site affects an integrase inhibitory activity. Therefore, the above analysis could not determine a site to be maintained and a site allowed to be modified for causing an integrase inhibitory activity.

Therefore, it cannot be recognized from the comparison between individual compounds described in the specification and prior art documents that a site other than the chelate ligand structure may be modified.

I Technical idea of each of the inventions

Plaintiff alleges that Group A, etc. test example compounds and Group B, etc. test example compounds are the compounds for which pharmacological data are disclosed as a compound representing a technical idea including a technical idea of each of the inventions.

However, even if the specification discloses that Group A, etc. test example compounds and Group B, etc. test example compounds are the compounds representing a generalized technical idea including a technical idea of each of the inventions, a person ordinarily skilled in the art could not recognize from the description of the specification and common general knowledge as of the filing date of

the original application that such generalization is not a simple speculation by an inventor as of the filing date of the original application. Specifically, a person ordinarily skilled in the art could not recognize that the technical idea of each of the inventions is included into a technical idea represented by Group A, etc. test example compounds and Group B, etc. test example compounds, the realization of such generalized technical idea results in a solution to a problem to newly provide a pharmaceutical composition including a compound having an integrase inhibitory activity.

(8) Summary

As described above, it cannot be said that the recitation of the scope of the claims according to each of the inventions conforms to the support requirement.

Therefore, the grounds 2 for rescission are groundless.

2. Conclusion

Therefore, the Patent should be invalidated, and the Plaintiff's request for seeking a rescission of the trial decision is groundless. Therefore, the Plaintiff's request shall be dismissed, and the court sentences as in the main text.

Intellectual Property High Court, First Division

Presiding Judge	TAKABE Makiko
Judge	SUGIURA Masaki
Judge	KATASE Akira

Attachment

Test example [Table 1]

Compound No.	IC_{50} (μg/ml)	Compound No.	IC_{50} (μg/ml)
A-7	0.76	C-26	0.36
A-12-a	0.33	C-39	0.23
A-17	0.80	D-5	0.45
A-17-c	0.94	E-8	0.14
A-50	0.16	E-16	0.12
A-141-k	0.68	F-4	0.57
A-158	0.67	G-7	0.48
B-6-a	1.6	H-7	0.68
B-6-d	2.4	I-4	0.50
B-12	0.29	J-4	0.26
B-12-b	0.21	K-4	0.57
B-29	0.12	L-4	0.49
B-68	0.22	M-6	2.9
C-22	0.48		