Trial Decision

Invalidation No. 2015-800226

Demandant	MSD K.K.
Patent Attorney	KUBOTA, Eiichiro
Patent Attorney	INUI, Yusuke
Patent Attorney	IMAI, Masahito
Patent Attorney	NAKAOKA, Kiyoko
Patent Attorney	YANO, Emiko
Demandee	Shionogi & Co. Ltd.
Patent Attorney	IWASAKI, Mitsutaka
Patent Attorney	TAMURA, Hiroshi
Patent Attorney	SHINAGAWA, Hisatoshi
Patent Attorney	OCHIAI, Kou
Patent Attorney	INAI, Fumio
Attorney	MAKINO, Tomohiko
Attorney	HORIGOME, Yoshinori
Attorney	KAJI, Azusako

The case of trial regarding the invalidation of Japanese Patent No. 5207392 entitled "ANTIVIRAL AGENT" between the parties above has resulted in the following

trial decision:

Conclusion

The correction of the scope of claims of Japanese Patent No. 5207392 shall be approved for Claims 1, 2, and 3 after correction as the Corrected Scope of Claims attached to the Written Correction Request.

The patent for the invention of Claims 1 to 3 of Japanese Patent No. 5207392 shall be invalidated.

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

Reason

No. 1. History of the procedures

The Japanese patent No. 5207392 for which the demand for invalidation trial was filed pertains to Japanese Patent Application No. 2009-57635 filed on March 11, 2009, which is a new patent application arising from the division of Japanese Patent Application No. 2003-521202 whose international filing date is August 8, 2002 (priority dates: August, 10, 2001, December 5, 2001, and June 28, 2002), and the establishment of patent right was registered on March 1, 2013, after submission of the Written Amendment received on April 3, 2012 and the Written Amendment received on August 9, 2012.

History of the procedures after the demand for invalidation trial is as follows:

December 27, 2015	Submission of Written Demand for Trial
February 16, 2016	Submission of Written Amendment from the Demandant
April 22, 2016	Submission of Written Reply and Written Correction request from the Demandee
April 25, 2016	Submission of Written Amendment from the Demandee
June 23, 2016	Submission of Written Refutation from the Demandant
Dated July 29, 2016	Written Notice (Written Notice of Proceeding Matters)
September 20, 2016	Submission of Oral Proceedings Statement Brief and Written Statement from the Demandant
September 20, 2016	Submission of Oral Proceedings Statement Brief from the Demandee
October 4, 2016	First Oral Proceeding
October 4, 2016	Submission of Written Statement from the Demandee
November 8, 2016	Submission of Written Statement (2) from the Demandee

December 13, 2016	Submission of Written Statement (2) from the Demandant
January 30, 2017	Submission of Written Statement (3) from the Demandee
Dated February 3, 2017	Advance Notice of Trial Decision
April 13, 2017	Submission of Written Correction Request and Written Statement (4) from the Demandee
May 31, 2017	Submission of Written Refutation (2) from the Demandant
Dated July 19, 2017	Decision to Approval or Disapproval of Amendment
July 19, 2017	Written Notice (Written Notice of Conclusion of Trial Proceedings)

No. 2. Request for correction

1. Object of request for correction

The request for correction by the Written Correction Request submitted on April 13, 2017 (hereinafter, referred to as "the Present Correction") requests the correction of the scope of claims attached to the application of Japanese Patent No. 5207392 as recited in the Corrected Scope of Claims attached to the Written Correction Request, as for Claims 1 to 3 after correction.

The request for correction by the Written Correction Request submitted on April 22, 2016 is deemed to have been withdrawn pursuant to the provisions of Article 134-2(6) of the Patent Act.

2. Contents of correction

Correction A-1

As for claim 1 of the scope of claims,

"a group represented by

...

(wherein Z^1 and Z^3 are each independently 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 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and

alkoxy));

Y is hydroxy;

Z is an oxygen atom;

R^C and R^D taken together with the neighboring carbon atoms form a 5- to 6-membered ring which may contain (a) heteroatom(s), and the ring may be a condensed ring with a benzene ring;

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);"

is corrected to

"(wherein 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 taken together with the neighboring carbon atoms form a 5- to 6-membered ring which may contain (a) heteroatom(s), and the ring may be a condensed ring with a benzene ring;
the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));."

Correction A-2

As for Claim 1 of the scope of claims,

"and the ring formed by R^C and R^D is .... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)"

is corrected to

"and the ring formed by R^C and R^D is .... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to carbon atom to which =Z is bonding"

Correction A-3

As for Claim 1 of the scope of claims,

"is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl."

is corrected to

"is optionally substituted with alkyl."

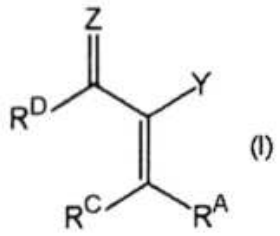
Correction B-1

As for Claim 2 of the scope of claims,

"A pharmaceutical composition of Claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing an N atom."

is corrected to

"A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the formula (I):
[Chemical Formula 1]

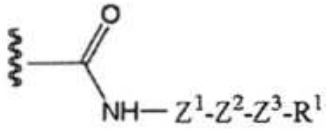


(I)

(wherein

R^A is a group represented by the formula:

[Chemical Formula 3]



(wherein Z^1 and Z^3 are each independently 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 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy))

Y is hydroxy;

Z is an oxygen atom;

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

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);

and the ring formed by R^C and R^D is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl, 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 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)),

a pharmaceutically acceptable salt thereof, or a solvated form thereof."

Correction B-2

Of the recitation corrected in the above Correction B-1,

"a group represented by

...

(wherein Z^1 and Z^3 are each independently 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 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));

Y is hydroxy;

Z is an oxygen atom;

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

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);"

is corrected to

"(wherein 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 taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing an N atom;

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));"

Correction B-3

Of the recitation corrected in the above Correction B-1,

"and the ring formed by R^C and R^D is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl, at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above))"

is corrected to

"and the ring formed by R^C and R^D is optionally substituted with an alkyl, at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above))."

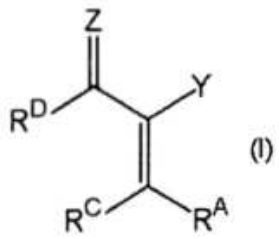
Correction C-1

As for Claim 3 of the scope of claims,

"A pharmaceutical composition of Claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s)."

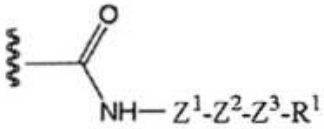
is corrected to

"A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the formula (I):
[Chemical Formula 1]



(I)

(wherein
R^A is a group represented by the formula:
[Chemical Formula 3]



(wherein Z^1 and Z^3 are each independently 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 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 optionally substituted heterocycle (each substituent of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));

Y is hydroxy;

Z is an oxygen atom;

R^C and R^D taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s);

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);

and the ring formed by R^C and R^D is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl, 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 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)),

a pharmaceutically acceptable salt thereof, or a solvated form thereof."

Correction C-2

Of the recitation corrected in the above Correction C-1,

"a group represented by

...

(wherein Z^1 and Z^3 are each independently 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 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));

Y is hydroxy;

Z is an oxygen atom;

R^C and R^D taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s);

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);"

is corrected to

"(wherein 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 taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s);

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));."

Correction C-3

Of the recitation corrected in the above Correction C-2,

"the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 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"

is corrected to

"the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 an optionally substituted phenyl, an optionally substituted 5- to 8-membered aromatic heterocyclic group, or an optionally substituted cycloalkyl with a carbon number of 3 to 6."

Correction C-4

Of the recitation corrected in the above Correction C-2,

"(each substituent of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy)"

is corrected to

"(each substituent of "optionally substituted" is independently selected from an alkyl, haloalkyl, halogen, and alkoxy; with the proviso that Z^1, Z^2, and Z^3 are not single bonds at the same time)."

Correction C-5

Of the recitation corrected in the above Correction C-2,

"is optionally substituted with a group represented by ...;"

is changed to

"is optionally substituted at the 3-position given that the carbon atom bonding to =Z is the 1-position with a group represented by ...;."

Correction C-6

Of the recitation corrected in the above Correction C-1,

"and the ring formed by R^C and R^D is ... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)"

is corrected to

"and the ring formed by R^C and R^D is ... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to carbon atom to which =Z is bonded)."

Correction C-7

Of the recitation corrected in the above Correction C-1,

"is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl)"

is corrected to

"is optionally substituted with alkyl)."

Correction C-8

Of the recitation corrected in the above Correction C-1,

"as an active ingredient a compound represented by ...,

a pharmaceutically acceptable salt thereof, or a solvated form thereof"

is corrected to

"as an active ingredient a compound represented by ...
(with the proviso that N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide is excluded),

a pharmaceutically acceptable salt thereof, or a solvated form thereof."

3. Judgment of suitability of correction

Correction A-1 is intended for restricting the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, to "4-fluorobenzyl."

In addition, in the description part of "the formula: $-Z^1-Z^2-Z^3-R^1$" with which the ring formed by R^C and R^D is optionally substituted, the correction specifically recites the content corresponding to the wording "the same as defined above" in the sentence "wherein ... are the same as defined above," in which the content thereof is omitted by citing a description of the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, in accordance with the above correction.

Therefore, Correction A-1 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act and for clarification of ambiguous statement stipulated in Article 134-2(1)(iii) of the Patent Act.

Furthermore, in paragraph [0018] of the Detailed Description of the Invention, "4-fluorobenzyl" is described as a group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A. In the description of Examples, compounds in which the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, such as Compound A-7, are 4-fluorobenzyl. Thus, Correction A-1 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction A-1 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Along with the above correction, regarding the position where "a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl" with which the ring formed by R^C and R^D is optionally substituted, Correction A-2 is intended for changing "at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)," to "at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to carbon atom to which =Z is bonding."

Therefore, Correction A-2 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

In addition to the general description in paragraphs [0006] to [0009] and [0020] of the Detailed Description of the Invention, in Examples, there are compounds, such as Compound A-7, in which "a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl" is substituted "at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to carbon atom to which =Z is bonding." Thus, Correction A-2 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction A-2 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction A-3 is intended for restricting "a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl" with which the ring formed by R^C and R^D is optionally substituted, to "alkyl."

Therefore, Correction A-3 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, in addition to the general description in paragraph [0021] of the Detailed Description of the Invention, in Examples, there are compounds, such as Compound A-7, in which "a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl" is "alkyl." Thus, Correction A-3 remains within the scope of the matters disclosed in the Patent Specification and does

not substantially enlarge or alter the scope of claims.

Therefore, Correction A-3 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction B-1 is intended for rewriting Claim 2 before Correction B-1, which cites Claim 1, to an independent claim that does not cite Claim 1.

Thus, Correction B-1 is intended for rewriting a claim which cites another claim to a claim that does not cite said other claim as stipulated in Article 134-2(1)(iv) of the Patent Act.

Furthermore, Correction B-1 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction B-1 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction B-2 is intended for further restricting the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A" to "4-fluorobenzyl" in Claim 2 after the correction with Correction B-1.

In addition, in the description part of "the formula: $-Z^1-Z^2-Z^3-R^1$" with which the ring formed by R^C and R^D is optionally substituted, the correction specifically recites the content corresponding to the wording "same meaning as above" in the sentence "where ... are the same as defined above," in which the content thereof is omitted by citing a description of the group represented by " the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, in accordance with the above correction.

Therefore, Correction B-2 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act and for clarification of ambiguous statement stipulated in Article 134-2(1)(iii) of the Patent Act.

Furthermore, Correction B-2 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction B-2 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction B-3 is intended for further restricting "a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl" with which the ring formed by R^C and R^D is optionally substituted, to "alkyl" in Claim 2 after the correction with Correction B-1.

Therefore, Correction B-3 is intended for restriction of the scope of claims

stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction B-3 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction B-3 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-1 is intended for rewriting Claim 3 before Correction C-1, which cites Claim 1, to an independent claim that does not cite Claim 1.

Thus, Correction C-1 is intended for rewriting a claim which cites another claim to a claim that does not cite said other claim as stipulated in Article 134-2(1)(iv) of the Patent Act.

Furthermore, Correction C-1 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-1 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-2 is intended for further restricting the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, to "4-fluorobenzyl" in Claim 3 after the correction with Correction C-1.

In addition, in the description part of "the formula: $-Z^1-Z^2-Z^3-R^1$" with which the ring formed by R^C and R^D is optionally substituted, the correction specifically recites the content corresponding to the wording "the same as defined above" in the sentence "where ... are the same as defined above," in which the content thereof is omitted by citing a description of the group represented by "the formula: $-Z^1-Z^2-Z^3-R^1$" in R^A, in accordance with the above correction.

Therefore, Correction C-2 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act and for clarification of ambiguous statement stipulated in Article 134-2(1)(iii) of the Patent Act.

In addition, Correction C-2 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-2 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-3 is intended for further restricting "the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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" in Claim 3 after the correction with Correction C-1, to "the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1 and Z^3 are each independently 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, or an optionally substituted cycloalkyl with a carbon number of 3 to 6."

Therefore, Correction C-3 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-3 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-3 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-4 is intended for further restricting "(each substituent of 'optionally substituted' is, independently from the others, selected from an alkyl, haloalkyl, halogen, and alkoxy)" in Claim 3 after the correction with C-1, to "(each substituent of 'optionally substituted; is, independently from the others, selected from an alkyl, haloalkyl, halogen, and alkoxy; with the proviso that Z^1, Z^2, and Z^3 are not single bonds at the same time)."

Thus, Correction C-4 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-4 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-4 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-5 is intended for restricting "is optionally substituted with a group represented by" to "is optionally substituted at the 3-position with a group represented by ... given that the carbon atom bonding to =Z is the 1-position;."

Thus, Correction C-5 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-5 remains within the scope of the matters disclosed in

the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-5 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-6 is intended for further restricting "and the ring formed by R^C and R^D is ... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)" in Claim 3 after the correction with Correction C-1, to "and the ring formed by R^C and R^D ... at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to carbon atom to which =Z is bonded)."

Thus, Correction C-6 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-6 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-6 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-7 is intended for further restricting "is optionally substituted with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl)" in Claim 3 after the correction with Correction C-1, to "is optionally substituted with alkyl.)"

Thus, Correction C-7 is intended for restriction of the scope of claims stipulated in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-7 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-7 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

Correction C-8 is intended for further restricting "as an active ingredient a compound represented by ..., a pharmaceutically acceptable salt thereof, or a solvated form thereof" in Claim 3 after the correction with Correction C-1, to "as an active ingredient a compound represented by ... (with the proviso that N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide are excluded), a pharmaceutically acceptable salt thereof, or a solvated form thereof."

Thus, Correction C-8 is intended for restriction of the scope of claims stipulated

in Article 134-2(1)(i) of the Patent Act.

Furthermore, Correction C-8 remains within the scope of the matters disclosed in the Patent Specification and does not substantially enlarge or alter the scope of claims.

Therefore, Correction C-8 falls under Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act.

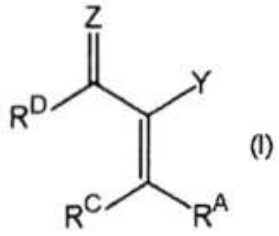
Accordingly, the corrections by the Present Correction consisting of Corrections A-1 to C-8 aim at matters prescribed in Article 134-2(1)(i), (iii), and (iv) of the Patent Act and complies with the provisions of Article 126(5) and (6) of the Patent Act, which is applied mutatis mutandis in the provisions of Article 134-2(9). Therefore, the Present Corrections shall be approved, as for Claims 1, 2, and 3 after correction.

Furthermore, Corrections B-1 and C-1 on corrected Claims 2 and 3 are intended for dissolving a citation relation between claims, and these corrections shall be approved. Then, since the Patentee requested that the corrected Claims 2 and 3 be treated as a correction unit different from Claim 1 when the corrections are approved, each of Claims 2 and 3 after correction is allowed to be corrected on a claim-by-claim basis.

No. 3. The Patent Invention

As a result of the above correction, the inventions of Claims 1 to 3 in the scope of claims of Japanese Patent No. 5207392 (hereinafter, respectively referred to as "Patent Invention 1" to "Patent Invention 3," and collectively referred to as "the Patent Invention") are specified by the matters recited in Claims 1 to 3 of the corrected scope of claims as follows:

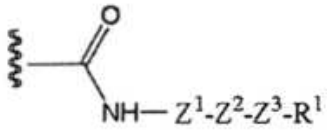
"[Claim 1]
A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the following formula (I):
[Chemical Formula 1]



(I)

(wherein
R^A is a group represented by the formula:

[Chemical Formula 3]



(wherein 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;

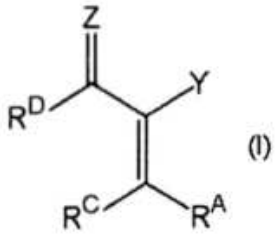
R^C and R^D taken together with the neighboring carbon atoms form a 5- to 6-membered ring which may contain (a) heteroatom(s), and the ring may be a condensed ring with a benzene ring;

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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, an optionally substituted cycloalkyl with a carbon number of 3 to 6, or an optionally substituted heterocycle (each substituent of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));

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

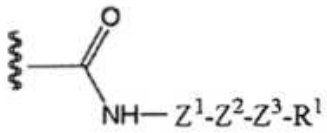
a pharmaceutically acceptable salt thereof, or a solvated form thereof.

[Claim 2]
A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the following Formula (I):
[Chemical Formula 1]



(I)

(wherein
R^A is a group represented by the formula:
[Chemical Formula 3]



(wherein 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;

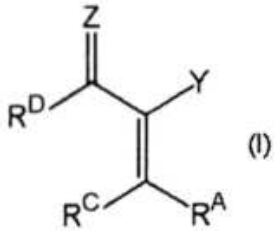
R^C and R^D taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing an N atom;

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 of 'optionally substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy));

and the ring formed by R^C and R^D is optionally substituted with an alkyl, at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)),

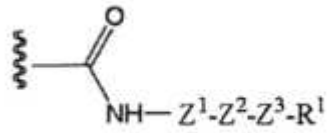
a pharmaceutically acceptable salt thereof, or a solvated form thereof.

[Claim 3]
A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the following Formula (I):
[Chemical Formula 1]



(I)

(wherein
R^A is a group represented by the formula:
[Chemical Formula 3]



(wherein 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 taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s);

the ring formed by R^C and R^D is optionally substituted at the 3-position given that the carbon atom bonding to =Z is the 1-position with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1 and Z^3 are each independently 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 of 'optionally-substituted' is independently selected from an alkyl, haloalkyl, halogen, and alkoxy; with the proviso that Z^1, Z^2, and Z^3 are not single bonds at the same time));

and the ring formed by R^C and R^D is optionally substituted with an alkyl, at a position other than a position that is substituted with the group represented by the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), and at a position adjacent to the carbon atom to which =Z is bonded)

(with the proviso that N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide is excluded),

a pharmaceutically acceptable salt thereof, or a solvated form thereof."

No. 4. The Demandant's allegation

In the Written Demand for Trial, the Demandant states as follows: the Demandant demands the decision, "the patent for the inventions recited in Claims 1, 2, and 3 in the scope of claims of Patent No. 5207392 shall be invalidated. The costs in connection with the trial shall be borne by the Demandee." The outline of the reasons for invalidation alleged by the Demandant is the following reasons for invalidations 1 to 4.

Furthermore, the Demandant submitted the following Evidences A No. 1 to No. 28 as a means of proof.

(1) Reasons for Invalidation

Reason for Invalidation 1

The Detailed Description of the Invention in the Specification for the Patent includes no statement about pharmacological test results showing that the compounds of Inventions 1 to 3 have integrase inhibitory activities. In fact, the compounds of Inventions 1 to 3 include compounds clearly having no non-integrase inhibitory activity. Thus, the Detailed Description of the Invention is not clear and sufficient to enable a person skilled in the art to carry out the Amended Invention.

Hence, the Patent has been granted on a patent application not complying with the requirements as provided in Article 36 (4)(i) of the Patent Act, and thus the Patent falls under Article 123(1)(iv) of the Act and should be invalidated (hereinafter, referred to as "Reason for Invalidation 1").

Note that, the Patent has been granted for a new patent application arising from the division of Japanese Patent Application No. 2003-521202 (hereinafter, referred to as "the original application"), and thus the reference date for determination regarding the requirement of Article 36(4)(i) of the Patent Act is August 8, 2002, which is the international filing date of the original application regarded as the filing date of the original application (hereinafter, "at the time of filing the present application").

The Demandant asserts Reason for Invalidation 1 as follows:

(The Demandant's Allegation 1)

"The Specification of the Patent Invention includes no statement about pharmacological test results showing that the Patent Invention has integrase inhibitory activities. Therefore, the Detailed Description of the Invention in the Specification of the Patent Invention is not clearly and sufficiently stated as to enable a person skilled in the art to work the Patent Invention." (the Written Demand for Trial, page 3, lines 7 to 11)

(The Demandant's Allegation 2)

"It is neither described nor suggested in the Present Specification or the like the patented compound is a 2-metal chelator type integrase inhibitor. In the first place, as Evidenced in Dr. Jay A. Grobler's written oath (Evidence A No 10), there are many compounds having the characteristics of a substituent having a 2-metal chelator structure and a ring structure at the end thereof but no integrase inhibitory activity. Thus, the patented compound does not serve as a 2-metal chelator type integrase

inhibitor. Therefore, a person skilled in the art could not understand from the description of the Specification that the compounds of the Patent Invention including the patented compound are two-metal chelator type inhibitors having integrase inhibitory activities." (the Written Refutation, page 18, line 13 to page 20, line 18)

(The Demandant's Allegation 3)

"At the time of the priority date for the Patent Invention, a person skilled in the art could not recognize that at least the structure, position, and shape of the active site of the HIV integrase are necessarily the same as or have the same characteristics as the structure, position, and shape of the active site of other integrases. In particular, the crystal structure of the HIV integrase was unknown at the time of the priority date for the Patent Invention. Therefore, the Demandee's allegation is unfounded in that a person skilled in the art at the time of the priority date for the Patent Invention could recognize that since two metal ions are present at the active site of the integrase of the trisarcoma virus, the same is also applied to the HIV integrase." (the Written Refutation, page 34, lines 9 to 18)

(The Demandant's Allegation 4)

"The enzyme assay is just a convenient starting point for sieving the compounds under test and is not sufficient for investigating the possibility of the inhibitory activity of such compounds. Although the Specification of the Patent states that the enzyme assay was performed, it does not indicate that the cell assay was willingly performed at all. Thus, a person skilled in the art coming into contact with the Specification of the Patent could not determine whether the compounds of the Patent Invention including the patented compound for which no cell assay has been performed actually have an effect as a pharmaceutical composition which is an integrase inhibitor." (the Written Refutation, page 37, line 19 to page 42, line 4)

(The Demandant's Allegation 5)

"In general, there are some cases in which pharmacological test results or the like are disclosed in the Specification and may be permitted to be complemented by submission of a Written Opinion, pharmacological test results, etc. after the filing of the application. However, it cannot be allowed to consider the pharmacological test results or the like submitted after filing of the application even when no objective supporting description of the pharmacological test results or the like is found in the Specification. This is because it should not be allowed, contrary to the purpose of the

patent system, which grants an exclusive right as a reward for the disclosure of the contents of the Patent Invention to the public (Intellectual Property High Court judgement, March 31, 2016 (2015 (Gyo-Ke) 10052)." (the Written Refutation, page 44, lines 3 to 9)

(The Demandant's Allegation 6)

"Even if the Demandee's counterarguments and Evidence are taken into consideration in the best interest of the Demandee, the following matters are only included in common general technical knowledge at the time of the priority date for the Patent Invention.

1. A compound having a chelator structure has promise as an integrase inhibitor.
2. A 'certain compound' that was thought to have integrase inhibitory activity may express integrase inhibitory activity by chelating its chelator structure to a divalent metal ion present in the active site of integrase.
3. The number of metal ions present at the active site of the HIV integrase may be two." (the Technical Explanation Material attached to the Oral Proceedings Statement Brief, page 4, top column)

(The Demandant's Allegation 7)

"The following matters were also common technical knowledge at the time of the priority date for the Patent Invention.

4. Even if a compound has a chelator structure or a substituent having a ring structure at the end, it often exerts no integrase inhibitory activity.
5. Even if a compound exhibits integrase inhibitory activity and also functions as an integrase inhibitor, many of other compounds similar in chemical structure to such a compound do not exhibit integrase inhibitory activity and do not function as integrase inhibitors. Difference of only one atom even can lead to the presence or absence of integrase inhibitory activity.
6. Although there were many candidates that could serve as integrase inhibitors, in fact, few compounds were effective as integrase inhibitors." (the Technical Explanation Material attached to the Oral Proceedings Statement Brief, page 4, bottom column)

(The Demandant's Allegation 7-1)

"Therefore, even if there is a general theory that amides and 1,3,4-oxadiazole are 'bioisostars' (although the Demandant does not accept such a general theory), a person skilled in the art could not understand or speculate that compound C-71, like compound

C-26, has integrase inhibitory activity based on this general theory and on the fact that compound C-26 is said to have integrase inhibitory activity.

...

However, as confirmed in the examination in the written oath, Merck #11 has an IC_{50} value of more than 100,000 nM and does not have integrase inhibitory activity, whereas compound D-9 has an IC_{50} value of 16,160 nM." (the Written Refutation (2), page 20, lines 10 to 25)

Reason for Invalidation 2

The Detailed Description of the Invention in the Specification for the Patent does not disclose the pharmacological test results that the compounds of Inventions 1 to 3 have integrase inhibitory activity. In fact, the compounds of Inventions 1 to 3 include compounds clearly having no integrase inhibitory activity, and thus the Detailed Description of the Invention does not state Inventions 1 to 3.

Therefore, the patent has been granted on a patent application not complying with the requirements as provided in Article 36(6)(i) of the Patent Act and falls under Article 123(i)(iv) of the Patent Act, and thus the Patent should be invalidated (hereinafter, referred to as "Reason for Invalidation 2").

The Demandant alleges Reason for Invalidation 2 as follows:

(The Demandant's Allegation 8)

"For the same reasons as aforementioned in the Reason for Invalidation 1, it cannot be said that the Specification states the Patent Invention." (the Written Demand for Trial, page 12, lines 14 to 17, the Written Refutation, page 45, lines 1 to 4)

Reason for Invalidation 3

Since the claims of priority rights (on August 10, 2001, December 5, 2001, and June 28, 2002) of the Patent Inventions 1 to 3 are not acknowledged, the reference date for determining the patentability shall be August 8, 2002 (the international filing date of the original application).

Since the Patent Inventions 1 to 3 are identical to the inventions disclosed in the Description originally attached to the Written Application of the patent application pertaining to Evidence A No. 3 (Japanese Patent Application No. 2003-537644, the international filing date October 21, 2002, and the claim of priority October 26, 2001 March 6, 2002, and the international publication date: May 1, 2003), the Patent has been

granted in violation of the provision of Article 29-2 of the Patent Act, and thus falls under Article 123(1)(ii) of the Patent Act. Therefore, the Patent should be invalidated (hereinafter, referred to as "Reason for Invalidation 3").

The Demandant makes the following allegations regarding the Reason for Invalidation 3.

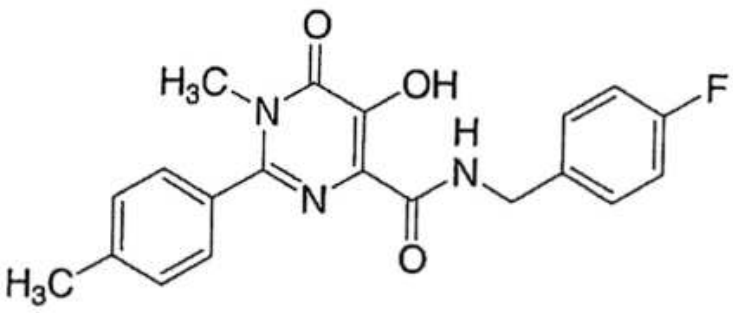
(The Demandant's Allegation 9)

"The Patent is accompanied by an internal priority claim based on three patent applications. In determining the patentability requirements stipulated in Article 29-2 of the Patent Act, an invention for which an internal priority claim is acknowledged is limited to an invention disclosed in the originally attached Description or the like relating to the application on which the internal priority claim is based. Thus, since not only the pharmacological test results but also even the manufacturing method of the invention having a structure in which the R^A portion is an NHCO group, including 'Compound C-71,' as in the Patent Invention are not disclosed in the originally attached Descriptions or the like of any of the basic applications on which the priority is claimed, the Invention is not disclosed in the originally attached Description or the like of any of the basic applications.

Therefore, the reference date for determining the patentability of the Patent is the original filing date of August 8, 2002." (the Written Demand for Trial, page 13, lines 3 to 23)

(The Demandant's Allegation 10)

"The Description originally attached to the Application at the time of filing of the patent application pertaining to Evidence A No. 3 (Japanese Patent Application No. 2003-537644) describes the following compound (hereinafter, referred to as 'Compound 18'):



, and also describes that Compound 18 is an integrase inhibitor, thereby describing an invention of a pharmaceutical composition which is an integrase inhibitor containing compound 18 as an active ingredient (hereinafter, referred to as 'the invention of Compound 18').

In addition, Compound 18 corresponds to the compound represented by Chemical Formula (I) recited in Claim 1 in the Patent Specification.

Therefore, the invention of Compound 18 is identical to the Patent Invention." (the Written Demand for Trial, page 12, line 19 to page 25, line 3 from the bottom)

(The Demandant's Allegation 11)

"The Description originally attached to the application at the time of filing of the patent application pertaining to Evidence A No. 3 (Japanese Patent Application No. 2003-537644) describes 'Compound 49,' 'Compound 32,' 'Compound 40,' 'Compound 41,' and 'Compound 52' (the descriptions of the respective chemical structural formulas are omitted), and also describes that these compounds are integrase inhibitors. Therefore, it describes that the inventions of pharmaceutical compositions as integrase inhibitors containing these compounds as active ingredients (hereinafter, referred to as 'the invention of Compound 49 or the like ').

In addition, these compounds correspond to the compounds represented by formula (I) in Claim 3 of the scope of claims after correction by the correction request.

Therefore, the invention of Compound 49 or the like is identical to Patent Invention 3." (the Written Refutation, page 4, line 18 to page 17, line 3)

Reason for Invalidation 4

Since the amendment by the Written Amendment received on April 3, 2012 limits the compounds of Claims 1 to 3 to only the compounds for which the pharmacological test results for having integrase inhibitory activity are not described, the amendment does not remain within the scope of the matters indicated in the Description, the Scope of Claims, or the Drawings originally attached to the Application of the Patent.

Therefore, the Patent has been granted on a patent application with an amendment that does not comply with the requirements provided in Article 17-2(3) of the Patent Act., and thus falls under Article 123(1)(i) of the Act and should be invalidated. (hereinafter, referred to as "Reason for Invalidation 4")

The Demandant makes the following allegations regarding the Reason for Invalidation 4.

(The Demandant's Allegation 12)

"When chemical substances are described in the form of a combination of a large number of alternatives by a Markush formula or the like in the originally attached Description or the like, as a result of removing alternatives by amendment, a particular combination of alternatives may remain in the claim and such alternatives may be the only alternatives. However, if it is not described in the originally attached Description or the like to adopt such a particular combination of alternatives, it is not acknowledged that the description of the originally attached Description or the like meant the adoption of such a particular combination of alternatives. Thus, such amendment is not allowed, because of adding a new matter. Applying this to the Patent, therefore, the amendment is not permitted simply by disclosing a compound having an NHCO group in the Present Specification. The compound having an NHCO group must be described herein as an 'integrase inhibitor.' Then, in order to be recognized that the pharmaceutical invention comprising a specific compound is disclosed in the Description, it is not enough that the pharmaceutical invention is formally described as a compound. At the very least, examples showing that the pharmaceutical invention achieves a pharmaceutical use, such as an example showing the results of a pharmacological test, must be disclosed." (the Written Demand for Trial, page 26, line 2 to page 28, line 25)

Reason for Invalidation 5

Claim 1 of the scope of claims after correction by the Written Correction Request dated April 13, 2017 recites "the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)." However, before this recitation, there are two recitations representing "the formula: $-Z^1-Z^2-Z^3-R^1$" but the contents of Z^1, Z^2, Z^3, and R^1 in one formula are different from those in the other formulas.

Then, the meaning of "the ... above" differs depending on which of the recitations before the above recitations means. Thus, it is not clear which recitation prior to this statement means "the ... above."

The same applies to the recitations in Claims 2 and 3.

Therefore, the recitations in the scope of claims after correction by the Written Correction Request dated April 13, 2017 is not clear. The Patent has been granted for a patent application not complying with the requirements stipulated in Article 36-6(2) of

the Patent Act, and thus falls under Article 123(1)(iv) of the Patent Act and should be invalidated. (hereinafter, referred to as "Reason for Invalidation 5")

Note that, Reason for Invalidation 5 is newly added to the reasons for the request in the Written Refutation (2) dated May 31, 2017, and changes the gist of the reasons for the request. However, as stated above, regarding the reason for invalidation newly added as a result of correcting the scope of claims by the Request for Correction dated April 13, 2017, Reason for Invalidation 5 is the result of the need to amend the reason for the claim and clearly has no risk of unreasonably delaying the trial examination. Therefore, pursuant to the provisions of Article 131-2(2) of the Patent Act, the body decided to approve the amendment to add Reason for Invalidation 5 in the Decision to Approval or Disapproval of Amendment dated July 19, 2017.

(2) Means of proof

Evidence A No. 1: Priority Certificate for International Patent Application PCT/GB/2002/004753 (including an attached copy of the Specification of US Patent Application 60/339,568)

Evidence A No. 2: International Publication No. WO 2003/35077

Evidence A No. 3: National Publication of International Patent Application No. 2005-511543

Evidence A No. 4: Written Amendment dated April 3, 2012 (Heisei 24) for the Patent

Evidence A No. 5: The Scope of Claims originally attached to the Application for the Patent

Evidence A No. 6: The Description originally attached to the Application for the Patent

Evidence A No. 7: International Publication No. WO 2002/30930

Evidence A No. 8: Decision of Rejection dated April 18, 2012 for the Patent

Evidence A No. 9: Written Demand for Appeal dated August 6, 2012 for the Patent

Evidence A No. 10: Dr. Jay A. Grobler's Oath dated January 27, 2014

Evidence A No. 11: Priority Document for the patent (Japanese Patent Application No. 2001-245071)

Evidence A No. 12: Priority Document for the patent (Japanese Patent Application No. 2001-370860)

Evidence A No. 13: Priority Document for the patent (Japanese Patent

Application No. 2002-191483)

Evidence A No. 14: Report by Professor Nouri Neamati (dated August 15, 2016)

Evidence A No. 15: Slide presentation entitled "Until New Antiviral Drug Is Made" by Akihiko Sato (creation date unknown)

Evidence A No. 16: Toshio Fujita et al., "Structural-Activity Correlation of Drugs-Guidelines for Drug Design and Mechanism Research," Nankodo Co., Ltd., January 10, 1979, pp. 1-3

Evidence A No. 17: Edited by C. G. Wermuth, "The Practice of medicinal chemistry," Technomic Co., Ltd., August 15, 1998, pp. 211-225,

Evidence A No. 18: Y. Pommier, et al., "INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS INTEGRASE," Advances in Virus Research, 1999 Vol. 52, pp. 427-458

Evidence A No. 19: J. Wai et al. "4-Alyl-2,4-dioxobutanoic Acid Inhibitors of HIV-1 Integrase and Viral Replication in Cells," Journal of Medicinal Chemistry 2000 Vol. 43 No. 26, pp. 4923-4926

Evidence A No. 20: D. Hazuda, et al., "Discovery and Analysis of Inhibitors of Human Immunodeficiency Integrase," Drug Design and Discovery 1997 15 (1), pp. 17-24

Evidence A No. 21: Written Brief dated August 3, 2016, prepared by the Demandee (Plaintiff No. 2)

(Note by the body: The "Plaintiff" is SHIONOGI & CO., LTD., and is the Demandee for the Trial.)

Evidence A No. 22: Report by Professor Nouri Neamati (dated August 14, 2015)

Evidence A No. 23: Report by Professor Zeger Debyser (dated July 29, 2016)

Evidence A No. 24: A. Pani, et al. "Anti-HIV-1 Integrase Drugs: How Far from the Shelf" Current Pharmaceutical Design, 2000, 6, pp. 569-584

Evidence A No. 25: Technical guide prepared in accordance with Section 7 of the Directive Order dated November 5, 2015 issued by Judge Armold J in the proceedings in Europe in relation to the Patent

Evidence A No. 26: Case No. HP-2015-000040 Judgment in the Patents Court of the Chancery Division of the High Court of Justice of England and Wales dated November 25, 2016, regarding the proceedings in Europe in relation to the Patent.

Evidence A No. 27: Decision of the Duesseldorf District Court of Germany dated October 6, 2016, regarding the proceedings in Europe in relation to the Patent. (case number unknown. Case of SHIONOGI vs MERCK SHARP & DOHME in relation to EP Patent No. 1422218)

Evidence A No. 28: Written Brief dated April 26, 2017, prepared by the Demandee (plaintiff No. 9)
(Note by the body: The "Plaintiff" is SHIONOGI & CO., LTD., and is the Demandee for the trial.)

No. 5 The Demandee's allegation

In the Written Reply dated April 22, 2016, the Demandee alleges that "the Demandee demands the trial decision such that the request for trial of the case was groundless. The costs in connection with the trial shall be borne by the Demandant," and then makes the allegations below for the respective Reason for Invalidation 1 to 4 alleged by the Demandant.

As means of proof, furthermore, the Demandee submitted Evidence B Nos. 1-1 to 1-16, Nos. 2 to 20, Nos. 20-1 to 20-2, and Nos. 21 to 68, and the translation of Evidence A No. 26 and the translation of Evidence A No. 27.

(1) Allegations against reasons for invalidation
Allegation against Reason for Invalidation 1

(The Demandee's Allegation 1)

"The Demandant alleges various reasons for invalidation, such as violation of Article 36 of the Patent Act. The main basis therefor is that the pharmacological data of the compounds stated in the scope of claims of the Patent (hereinafter referred to as 'the Patent Compound') is not described in the Specification of the Patent.

However, the Description at the time of filing the application of the Patent describes a comprehensive group of compounds including the Patent Compound (hereinafter referred to as 'the Patent Invention Compounds'). A person skilled in the art could clearly understand that the Patent Invention compounds are binuclear cross-linked tridentate ligand (2-metal chelator) type inhibitors that inhibit integrase activity by coordinating to two metal ions present in the active center of integrase. Furthermore, there are abundant pharmacological data about the Patent Invention Compounds in the Specification of the Patent. A person skilled in the art could easily understand that the Patent Compound has an integrase inhibitory effect as well as the compounds for which these pharmacological data are specified." (the Written Reply, page 5, line 16 to page 6, line 7)

(The Demandee's Allegation 2)

"It has been known that integrase is an enzyme (metal enzyme) that has a metal ion in the active center and makes this an essential factor for the expression of activity (Evidence B No. 1-5)." (the Written Reply, page 11, lines 11 to 13)

(The Demandee's Allegation 3)

"A polydentate ligand that forms a chelate is a chelate ligand (hereinafter referred to as a 'chelator')" (the Written Replay, page 12, lines 9 to 10)

(The Demandee's Allegation 4)

"At the time of the priority date for the Patent Invention (August 2001), as an inhibitor of integrase, a chelator-type inhibitor was a promising candidate (Evidence B No. 1-6). The following are known for chelator-type integrase inhibitors whose activities have been confirmed (for details, see Attachment 1 of Evidence B No. 1-1 (Professor Koike's Written Opinion) and Evidence B Nos. 1-7 to 11). ... In addition to the chelator moiety, any of these inhibitors had a substituent with a ring structure at the end (blue dashed lines in Figs. 5 and 6 below)." ('the Written Reply, page 13, lines 3 to 7)

(The Demandee's Allegation 5)

"The present inventors ... have found that open-chain compounds that exhibit relatively excellent integrase inhibitory activity have commonly have a binuclear cross-linked tridentate ligand structure and a substituent having a ring structure at the end (blue dashed lines in Figures 5 and 6 above). On the other hand, since there are two metal ions in the active center of the integrase of avian sarcoma virus, which has an integrase like HIV, the idea that the number of metal ions present in the active center of the HIV integrase is not one but two has become influential (Evidence B Nos. 1, 12 to 15). Based on these findings, as a chelator partial structure, a 2-metal chelator-type structure in which the coordinating atoms are serially connected in the same direction by the cyclic structure on the back side (see Figure 7 below and see the symbols in the figure above) was adopted, and combined with a substituent having a ring structure at the end to complete the Patent Invention (Note 3). The Patent Invention Compounds are roughly divided into two basic structures (Note 4) shown in Figure 7 below. As stated in detail below, they have in common a characteristic structure (red solid line) as a binuclear cross-linked tridentate ligand (hereinafter referred to as '2-metal chelator') that chelates to two metal ions, and a substituent with a ring structure at the end ($-Z^1-Z^2-Z^3-R^1$; blue dashed line)." (the Written Reply, page 15, lines 5 to 23)

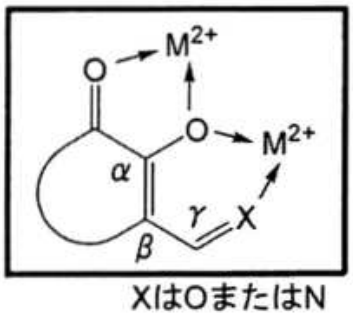
(The Demandee's Allegation 6)

"As stated below, this characteristic structure, the two-metal chelator moiety, forms the basis of the integrase inhibitory action of the Patent Invention Compounds.

...

(1) The structure of chelator moiety that is the basis of the Patent Invention Compounds ... these three functional groups can inactivate the enzyme activity of the integrase by forming a chelate with two divalent metal ions (M^{2+}) coordinated to the integrase enzyme.

Figure 8



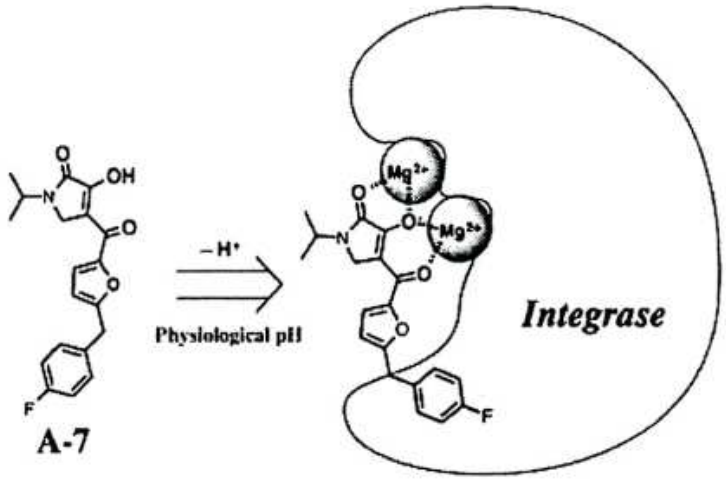
ＸはＯまたはＮ　X is O or N

(2) An important feature of the Patent Invention Compounds are that the carbon atom of the first carbonyl group and the carbon atom at the β-position in the above structure of the moiety form a 5- or 6-membered cyclic structure on the back side of the moiety structure capable of forming a chelate. ... Later, the simultaneous effects of these three coordinating atoms in the same direction were demonstrated in an academic paper (Evidence B No. 3).

(3) Further, the Patent Invention Compounds are also characterized in that, as will be stated later, at least one among the cyclic structure on the back side of Figure 8 above, C ring, and R^B is substituted with the substituent ($-Z^1-Z^2-Z^3-R^1$) having a ring structure at the terminal. However, this substituent is also found in conventional integrase inhibitors. Thus, the inhibitor will exert better activity by having such a substituent in addition to the 2-metal chelator structure.

(4) The mechanism of the integrase inhibitory action of the Patent Invention Compounds is illustrated below, taking Compound A-7 of the Example as an example, (Evidence B No. 1-1).

Figure 9



" (the Written Reply, page 16, line 1 to page 18)

(The Demandee's Allegation 7)

"A person skilled in the art could understand that the Patent Compound has an integrase inhibitory effect from the entire description and pharmacological data of the Specification of the Patent by taking into account the common general technical knowledge at that time." (the Written Reply, page 23 lines 3 to 5)

(The Demandee's Allegation 8)

"B Regarding the common general technical knowledge at the time of the priority date for the Patent Invention

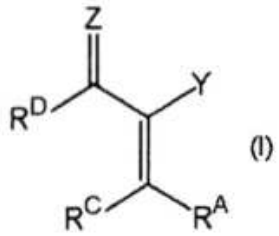
As stated in the above III, 2 and 3, at the time of August 2001 (the priority date for the Patent Invention), integrase was known as an enzyme having a metal ion in the active center (Evidence B No. 1-5). A chelator-type inhibitor was a promising candidate for the inhibitor (Attachment 1 of Evidence B No. 1-1 (Professor Koike's Opinion)).

In addition, as stated in the above IV, 1, as of August 2001, the idea that the number of metal ions present in the active center of integrase is not one but two has become influential." (the Written Reply, page 24, lines 17 to 23)

(The Demandee's Allegation 9)

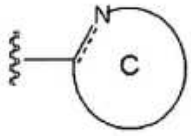
"The Specification of the Patent (Evidence A No. 6, Note 6) describes the characteristic features (1) to (4) of the compounds of the present invention (Note by the body: In the original text, they are indicated by circled numbers, and the same applies

hereafter) as below. For a person skilled in the art who have the common general technical knowledge like the above B, the descriptions of these features (1) to (4) are conscious of the integrase inhibitor, which is a 2-metal chelator compound:
(1) having a basic structure represented by the following formula (1):

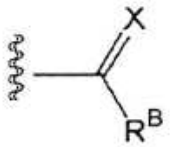


(I)

(2) wherein Z and Y are O, OH, etc. (paragraph 0018, items (2) and (3)), and R^A is a nitrogen-containing cyclic structure :



having an unsubstituted nitrogen adjacent to the substituent bond,
or a substituent $C(=X)R^B$:



having a C=X group (X is O, etc.) adjacent to the bond of the substituent
(the same paragraph, items (4) to (6)),
(3) R^C and R^D taken together with the neighboring carbon atoms form a ring structure (the same paragraph, item (1)), and
(4) at least one among the R^C/R^D ring, C ring, or R^B is substituted with $-Z^1-Z^2-Z^3-R^1$ (the same paragraph, item (8)),

In other words, regarding the above features (1) and (2), it is clear that a person skilled in the art would recognize that the moiety structure formed by Z, Y, and N or C=X in R^A is a tridentate ligand (2-metal chelate) structure which is coordinated to two metal ions existing in the active center of the integrase. Although the Specification of the Patent does not specify that the above moiety structure is a chelator moiety, it is common general technical knowledge from before August 2001 that O in =O or OH, S in -SH, and unsubstituted N in -NH or aromatic heterocycles are coordination atoms

with unshared electron pairs. Therefore, a person skilled in the art could understand that the above moiety structure is a structure peculiar to the tridentate ligand and has a chelating ability for two metal ions existing in the active center of integrase. (Evidence B No. 1-1 (Professor Koike's Opinion)).

Regarding the above feature (3), R^C and R^D form a planar cyclic structure with adjacent carbon atoms and located on the back side of the tridentate ligand moiety (2-metal chelator moiety) to regulate its freedom of configuration. Thus, a person skilled in the art could understand that it contributes to the direction control of the coordination atom of the 2-metal chelate moiety. (Evidence B No. 1-1 (Professor Koike's Opinion)).

The substituent ($-Z^1-Z^2-Z^3-R^1$) of the above feature (4) is characterized by having a ring structure at the end, and is also found in conventional integrase inhibitors (Attachment 1 of Evidence B No. 1-1 (Professor Koike's Opinion)). The Patent Invention Compounds exhibit better activity by having such a substituent in addition to the 2-metal chelator structure (Evidence B No. 1-1: Professor Koike's Opinion).

Therefore, a person skilled in the art who read the Specification of the Patent could understand that the Patent Invention Compounds have the characteristics adopting a 2-metal chelator structure (the above features (1) to (3)) in which coordination atoms are arranged in the same direction on the back side by the cyclic structure, in the combination of the chelator structure and the substituent having a ring structure at the end (the above feature (4)).

In the Specification of the Patent, furthermore, a wide variety of structures, such as those of the nitrogen-containing cyclic structure and R^B of (2) and the R^C/R^D ring of (3), are described as examples, and particularly R^B is disclosed as a possible substituent with an extremely diverse structure (paragraph 0018, items (7) and (10)) (Written Reply, page 25, line 3 to page 27, line 7)

(The Demandee's Allegation 10)

"The integrase inhibitory effect of the Patent Compound is also supported by pharmacological test data after filing of the application for the Patent.

In the examination of this application, pharmacological data have been submitted for four compounds included in the Patent Compound (Evidence B No. 9: Written opinion) and 12 compounds have actually been confirmed to have integrase inhibitory effects (Evidence B No. 10: Yoshinaga Report). From these pharmacological data, it is clear that the Patent Compound actually has an integrase inhibitory effect, sufficiently supporting that the Patent meets the enablement requirements." (Written Reply, page 33, lines 8-16)

(The Demandee's Allegation 11)

"This point is also valid in the technical field of the integrase inhibitor of the Patent Invention, as the body points out. Specifically, as stated in detail in the Written Reply, in the case of the integrase inhibitor of the Patent Invention, the substructures that affect the mechanism of action are (1) a 2-metal chelator structure in which coordination atoms are arranged in the same direction on the back side by the cyclic structure; and (2) a substituent having a ring structure at the end. If they are common, they may have an integrase inhibitory effect even if the remaining structure changes. In particular, as stated in Evidence B No. 21-1 (Proceedings A30-1) (Professor Koike's written opinion at Hiroshima University Graduate School: Koike's written opinion 2), which will be explained later, it is a matter of common general technical knowledge that the binding force of chelated coordination bonds is strong. Therefore, as long as the above moiety structures (1) and (2) (particularly the moiety structure (1), which is a 2-metal chelator structure) are retained, it can be reasonably expected to have an integrase inhibitory action regardless of differences in other structures.

On the other hand, when a compound has an overall chemical structure similar to that of the Patent Invention Compound at first glance, but different in above partial structures (1) and (2), the compound may have a significantly reduced integrase inhibitory effect. Evidence A No. 10 (Grobler's written oath) submitted by the Demandant is just such an example. (Oral proceedings statement brief, page 7, line 2 from the bottom to page 8, line 13)

(The Demandee's Allegation 12)

"The common general technical knowledge at the time of the priority date for the Patent Invention

(1) (Note by the body: In the original text, they are indicated by circled numbers, and the same applies hereafter) It was widely known that the active center of HIV integrase has a metal ion, and the number of the metal ion is two.

(2) As an integrase inhibitor, a chelator-type was promising.

(3) Many chelator-type integrase inhibitors had a substituent (Z^1-Z^2-Z^3-R^1) having a ring structure at the end in addition to the chelator moiety.

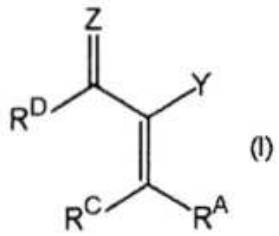
(4) As a premise of (1) and (2), there was the following general technical knowledge regarding chelation.

- Typical structure of chelate compound
- The chelate bond has a strong binding force comparable to that of a covalent bond."

(the Technical Explanation Material attached to the Written Statement dated on October 4, 2016, column 17)

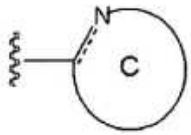
(The Demandee's Allegation 13)

"The characteristic features (a) to (d) of the Patent Invention Compounds :
(a) having a basic structure represented by the following formula (1)

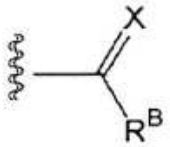


(I)

wherein Z and Y are O, OH, etc., and R^A is



or



(c) R^C and R^D taken together with the neighboring carbon atoms form a ring structure,
(d) at least one among the R^C/R^D ring, C ring, and R^B is substituted with $-Z^1-Z^2-Z^3-R^1$"
(column 25 of the Technical Explanation Material attached to the Written Statement dated October 4, 2016)

(The Demandee's Allegation 14)

"Considering the common general technical knowledge (1) to (4), it can be understood that a wide variety of compounds having the characteristics (a) to (d) of the Patent Invention Compounds described in the Specification have integrase inhibitory activities, and that the Patent Compound is an example thereof, and it can be said that the Detailed Description of the Invention is clearly and sufficiently describes so that a person skilled in the art could carry out the Patent Invention.

In such a case, the Certificate of Experimental Results is allowed to support the allegation." (column 39 of the Technical Explanation Material attached to the Written

Statement dated October 4, 2016)

(The Demandee's Allegation 15)

"(a) In the Patent Invention, the reason why the above various structures commonly play an integrase inhibitory action is none other than the fact that the central structure of the mechanism of action, which is the chelator structure, has been determined. Therefore, as long as it has a 2-metal chelator structure like the Patent Invention compound, it is theoretically unlikely that it exerts no integrase inhibitory action caused by the chelator effect at all (the effect is 'zero (0)'). This point is as stated in the above Evidence B No. 21-1." (Oral Proceedings Statement Brief dated September 20, 2016, page 31, lines 6 to 4 from the bottom)

(The Demandee's Allegation 16)

"(b) As stated above, as long as it has a 2-metal chelator structure, it is theoretically unlikely that it exerts no integrase inhibitory action caused by the chelator effect at all (the effect is '0').

Moreover, the Patent Invention Compound is actually provided with not only a 2-metal chelator structure but also structural features: (1) a back ring 2-metal chelator structure; and (2) a substituent having a ring structure at the end, thereby preserving a practical integrase inhibitory effect. After the filing of the Patent Invention, the structure of the active center of integrase has been clarified, and as a result, the mechanism of the integrase inhibitory action of the Patent Invention based on the above (1) and (2) has been proved." (Oral proceedings statement brief dated September 20, 2016, page 33, line 5 from the bottom to page 34, line 4)

(The Demandee's Allegation 17)

"Thus, even if the IC_{50} exceeds 100 μM, it only indicates that the activity is relatively low and does not mean no activity.

In addition, the fact that the IC_{50} exceeded 100 μM (100,000 nM) in the enzyme inhibition test conducted by Dr. Grobler means that no experiment was conducted at a concentration higher than 100 μM as 50% inhibition could not be achieved even at a concentration of 100 μM, and thus does not mean that 50% inhibition could not be achieved no matter how much the concentration was increased above 100 μM. Incidentally, in the example of Evidence B No. 31 (Proceedings A35) citing the graph above, the measurement was carried out at up to 1000 μM.

As stated above, the Demandant's allegation that the 17 different compounds are

determined inactive based on the IC_{50} value stated in Dr. Grobler's oath (Evidence A No. 10) is clearly groundless." (Oral Proceedings Statement Brief dated September 20, 2016, page 42, lines 3 to 14)

(The Demandee's Allegation 18)

"Understanding the Specification of the Patent does not require scientific substantiation of the common general technical knowledge (1) and (2). It is sufficient for a person skilled in the art to understand them with sufficient rationality. That is, the description of the Patent specifies that a typical 2-metal chelator structure is essential, and describes a wide variety of specific compounds that can be seen at first glance as being of a two-metal chelator structure. Therefore, if a person skilled in the art could understand that a model in which the number of metal ions present in the active center of HIV integrase is two has been widely known and the conventional promising integrase inhibitors can exert their inhibitory effects by chelating to divalent metal ions, the person skilled in the art would sufficiently understand that the reason why sufficient pharmacological data have been obtained for various compounds having different structures is that the Patent Invention Compound exerts an integrase inhibitory action as a two-metal chelator. This does not depend on the model of two metal ions and whether or not the integrase inhibitor has been demonstrated to actually chelate to the active center of the integrase." (Written Statement (2) dated November 8, 2016, page 9, lines 1 to 13)

(The Demandee's Allegation 19)

"On the other hand, as the Demandant admits, a person skilled in the art at the time of the priority date for the Patent Invention had recognized that Patent Invention Compound had a 2-metal chelator structure based on the description of the Patent and the common general technical knowledge. Therefore, a person skilled in the art in light of the above pharmacological data could understand that the moiety contributing to the integrase inhibitory activity in the substituent R^A of the Patent Invention compound is an unsubstituted nitrogen atom or an oxygen atom (arrow in the above figure) serving as a chelating ligand, and as long as it is maintained the rest has some structural freedom." (Written Statement (2) dated November 8, 2016, page 20, the last line to page 21 line 5)

(The Demandee's Allegation 20)

"Regarding the Patent Invention Compound, in addition to the pharmacological

data for 27 compounds in the Specification of the Patent, it has been confirmed that a huge number of compounds for which production examples are described also have integrase inhibitory effects (Evidence B No. 8)." (Written Reply, page 30, lines 3 to the last line)

(The Demandee's Allegation 21)

"Pharmacological data for 120 compounds different from the compounds whose manufacturing methods are stated in the Specification of the Patent are submitted as Evidence B No. 28.

A total of 383 compounds of the Patent Invention are extremely diverse in structure except that they all exhibit the activity and share a common structure in that each of them has a back ring 2-metal chelator structure and a substituent having a ring structure at the end. From this fact, it is clear that the activity can be obtained in common for compounds having a wide variety of structures if they have the characteristics stated in the Specification of the Patent." (Oral Proceedings Statement Brief dated September 20, 2016, page 28, lines 15 to 25)

(The Demandee's Allegation 21-1)

"As is clear at first glance, the chemical structure of Compound 1 of the Corrected Invention has a structure very similar to the structures of 27 compounds whose pharmacological data are described in the Specification of the Patent.

...

Therefore, the difference between the structure recited in the Corrected Invention and the structure of the compound in which the pharmacological data are described is that the substituent portion (blue line in the figure) of R^A is an amide in the former, whereas a nitrogen-containing heterocycle, aryl ketone, or heteroaryl ketone in the latter." (Written Statement (3), page 10, line 11 to page 13, line 9)

(The Demandee's Allegation 21-2)

"From the above, Professor Kikai states that he could recognize the matters cited below from 27 compounds in groups A to M for which pharmacological data were represented.

(a) The degree of freedom of the core itself is high, and a 5- or 6-membered ring which may contain (a) heteroatom(s) and a condensed ring of these rings and a benzene ring can be used as the core.

(b) What the 27 compounds have in common are the approximate positions of the

oxygen atom or the unsubstituted nitrogen atom of an oxo group on the core, a hydroxy group at an adjacent position thereof, and an -C(=O)- R^B or a nitrogen-containing aromatic heterocycle at the adjacent position thereof (the unsubstituted nitrogen atom is located at a position adjacent to the atom having a bond).
(c) Considering the above superposition figure, the R^B itself of -C(=O)-R^B is not limited to a ring, and other groups may also have an integrase inhibitory action.
(d) It is common to 27 compounds that at least one among the ring formed by R^C and R^D, C ring, or R^B is substituted with the 4-fluorobenzyl group or the like." (Written Statement (3), page 20, line 21 to page 21, line 7)

(The Demandee's Allegation 21-3)

"In addition, the Compound 1 of the Corrected Invention is limited to the extent that it does not include the compound alleged by the Demandant to be inactive (Evidence A No. 10)." (Written statement (3), page 23, lines 6 to 7)

(The Demandee's Allegation 21-4)

"(1) Advance Notice of Trial Decision denied all the common general technical knowledge alleged by the Demandee as a premise for understanding the Specification of the Patent. However, at least the following matters would be naturally known to a person skilled in the art engaged in the research and development of integrase inhibitors, and are thus not alleged by the Demandant (Demandant's written statement (1) dated September 20, 2016, page 5, line 1 to page 8, the last line).
(1) The integrase has a divalent metal ion at the active center that plays a central role in the enzyme activity (Evidence B No. 23 and Evidence B No. 24).
(2) A chelate bond to a divalent metal ion at the active center of integrase has been proposed as a mechanism for exerting the inhibitory activity of an integrase inhibitor (Evidence B No. 1-6, Evidence B No. 1-7, Evidence B No. 24, Evidence B No. 25, and Evidence B No. 26).
...

On the other hand, the model in which the number of metal ions in the active center of integrase is two is specified in a book on a collection of review articles (Evidence B No. 23) and a book on virus studies, and, at that time, was known by a person skilled in the art. Therefore, a person skilled in the art could reasonably understand that a structure, which can function as a tridentate ligand that chelates to two metal ions in Compound 1 of the Corrected Invention, is essential as one being coincident with the model stated in review articles and the like." (Written Statement (3),

page 26, line 25 to page 30, line 6 from the bottom)

(The Demandee's Allegation 21-5)

"Here, the fact that amide and 1,3,4-oxadiazole are equivalent as so-called bioisosteres is stated in the review article Evidence B No. 65, and are well known to a person skilled in the art." (Written Statement (3), page 35, lines 1 to 3)

Allegation against Reason for Invalidation 2

(The Demandee's Allegation 22)

"For the same reasons as the counterargument to Reason for Invalidation 1, it is clear that the description of the Patent states the Patent Invention." (Written Reply, page 39, lines 6 to 15)

Allegation against Reason for Invalidation 3

(The Demandee's Allegation 23)

"A person skilled in the art could manufacture the Patent Compound based on the common general technical knowledge at the time of the first basic application and the description in the Description of the first basic application. A person skilled in the art could also understand that the Patent Compound had pharmacological activity. Therefore, the Patent can enjoy the priority of the first basic application (filed on August 10, 2001)." (Written Reply, page 40, lines 17 to 21)

(The Demandee's Allegation 24)

"The Patent can enjoy the benefit of priority under the first basic application, and the reference date for determining the patent requirements of the Patent Invention is August 10, 2001, which is the filing date of the first basic application. Therefore, the Specification of US 568 Application (Evidence A No. 1) filed on October 26, 2001 does not qualify as a prior application based on the provisions of the prior art effect (Article 184-13(1) of the Patent Act and Article 29-2 of the Patent Act)." (Written Reply page 44, lines 18 to 17)

Allegation against Reason for Invalidation 4

(The Demandee's Allegation 25)

"The only substantive reason the Demandant alleges the addition of new materials is that the pharmacological test data for the Patent Compound are not included in the Specification of the Patent.

However, even if the pharmacological test data may be discussed as a matter of enablement requirements, it does not matter whether or not new matters are added, except when the pharmacological test data itself is corrected." (Written Reply, page 45, lines 16 to 25)

(The Demandee's Allegation 26)

"Whether or not the amendment corresponds to the addition of new matters should be judged by whether or not the amendment introduces new technical matters. Thus, since the compounds before and after the amendment as integrase inhibitors have the same characteristic features, it is clear that the amendment does not introduce any new technical matters." (Written Reply, page 46, lines 7 to 20)

(2) Means of proof

Evidence B No. 1-1: Written opinion created on February 22, 2016 by Dr. Toru Koike (Professor, Hiroshima University Graduate School)

Evidence B No. 1-2: Shoji Nakahara and Osamu Shibata, Ed., "Kagaku no Ryoiki (Area of Chemistry)," Special Issue No. 90, Nankodo Co., Ltd., published on May 30, 1970, pp. 101-138 (Evidence B No. 1-1, Attachment 1)

Evidence B No. 1-3: A. Scozzafava, C. T. Supuran, J. Med. Chem. 2000 43 pp. 3677-3687 (published on October 5, 2000, Evidence B No. 1-1, Attachment 2)

Evidence B No. 1-4: M. Cheng et al., J. Med. Chem. 2000 43 pp. 369-380 (published on February 10, 2000, Evidence B No. 1-1, Attachment 3)

Evidence B No. 1-5: F. Dyda et al., Science 1994, Vol. 266, pp. 1981-1985 (Evidence B No. 1-1, Attachment 4)

Evidence B No. 1-6: Y. Pommier et al., Antiviral Res., 2000, vol. 47, pp. 139-148 (published on September 2000, Evidence B No. 1-1, Attachment 5)

Evidence B No. 1-7: N. Neamati et al., J. Med. Chem. 1998, vol. 41, pp. 3202-3209 (Evidence B No. 1-1, Attachment 6)

Evidence B No. 1-8: International Publication No. WO 1999/50245 (Evidence B No. 1-1, Attachment 7)

Evidence B No. 1-9: D. J. Hazuda et al., Science 2000, Vol. 287, pp. 646-650 (published on January 28, 2000, Evidence B No. 1-1, Attachment 8)

Evidence B No. 1-10: International Publication No. WO 2000/39086 (published

on July 6, 2000, Evidence B No. 1-1, Attachment 9)

Evidence B No. 1-11: International Publication No. WO 2001/017968 (published on March 15, 2001, Evidence B No. 1-1, Attachment 10)

Evidence B No. 1-12: G. Bujacz et al., THE JOURNAL OF BIOLOGICAL CHEMISTRY, 1997 Vol. 272, p. 18161 to 18168 (Evidence B No. 1-1, Attachment 11)

Evidence B No. 1-13: J. Lubkowski et al., THE JOURNAL OF BIOLOGICAL CHEMISTRY, 1998 Vol. 273, pp. 32685 to 32689 (Evidence B No. 1-1, Attachment 12)

Evidence B No. 1-14: A. B. Hickman et al., Molecular Cell, 2000 vol. 5, pp. 1025-1034 (published on June 1,2000, Evidence B No. 1-1, Attachment 13)

Evidence B No. 1-15: P. A. Rice, T. A. baker, Nature Structural Biology 2001 Vol. 8, pp. 302-307 (published in April 2001, Evidence B No. 1-1, Attachment 14)

Evidence B No. 1-16: T. A. Steitz, J. A. Steitz, Proc. Natl. Acad. Sci. 1993 90 pp. 6498-6502 (Evidence B No. 1-1, Attachment 15)

Evidence B No. 2: Rokuro Kuroda et al., Analytical Chemistry, published on October 30, 1993, pp. 88-91

Evidence B No. 3: T. Kawasuji et al., Biooroganic & Medicinal Chemistry 2007 vol. 14, pp. 5487-5492 (published on August 15, 2007)

Evidence B No. 4: Notice of reasons for refusal dated March 31, 2009 in the examination of the original application of Japanese Patent Application No. 2009-57635 (Japanese Patent Application No. 2003-521202) for the Patent

Evidence B No. 5: Written amendment dated May 15, 2009 in the examination of the original application of Japanese Patent Application No. 2009-57635 (Japanese Patent Application No. 2003-521202) for the Patent

Evidence B No. 6: Written amendment dated August 9, 2012 for the Patent

Evidence B No. 7: Tadashi Sasaki, "Sayo Bunshisekkei (Action Molecule Design)," Nankodo Co., Ltd., published on May 1, 1974, pp. 9

Evidence B No. 8: Report (1) by Dr. Tomoichi Yoshinaga, created on February 22, 2016

Evidence B No. 9: Written statement dated April 3, 2012 for the Patent

Evidence B No. 10: Report (2) by Dr. Tomoichi Yoshinaga, created on February 22, 2016

Evidence B No. 11: Case Law of The Boards of Appeal of the European Patent Office, European Patent Office, published in September 2013 (European Patent Office "Trends in trial decisions," 7th edition (Chapter II, C, "Sufficiency of Disclosure")

Evidence B No. 12: Manual of PATENT EXAMINING PROCEDURE (MPEP)

(section 2164.05) Chapter 2100, the United States Patent and Trademark Office, published in November 2015

Evidence B No. 13: Interim Decision dated March 31, 2015 in the examination procedure for opposition to European Patent Application No. 02749384.0 corresponding to Japanese Patent Application No. 2009-57635 for the Patent.

Evidence B No. 14: Claims after amendment dated March 12, 2015 in the examination procedure for opposition to European Patent Application No. 02749384.0 corresponding to Japanese Patent Application No. 2009-57635 for the Patent

Evidence B No. 15: K. P. C. Vollhardt, N. E. Schore, "Vollhardt/Schore Gendai Yuki Kagaku (Organic Chemistry: Structure and Function) (2nd vol.)," published by Kagaku-Dojin Co., Ltd., August 10, 1996, pp. 811-825

Evidence B No. 16: Z. D. Liu et al., Bioorganic & Medicinal Chemistry, 2001 9(3) pp. 563-573 (published in March 2001)

Evidence B No. 17: R. W. Taft et al., Journal of the American Chemical Society 1963 85(20) pp. 3146-3156

Evidence B No. 18: T. W. Greene, pp. G. M. Wuts, "Protective Groups in Organic Chemistry Third Edition," John Wiley & Sons, Inc., published in 1999, pp. 266-269

Evidence B No. 19: Sing-Yuen Sit et al., Bioorganic & Medicinal Chemistry Letters 1996 6(5) pp. 499-504

Evidence B No. 20: V. L. Gein et al. (the title of the article in Russian characters omitted), Zhurnal Obshchei Khimii 1993 63 (10) pp. 2324-2328

Evidence B No. 21-1: Written opinion created on July 20, 2016 by Dr. Toru Koike (Professor, Hiroshima University Graduate School)(Written statement of Koike 2)

Evidence B No. 21-2: Hiroshi Nagatomi and Hisashi Yamamoto, Ed., "Soyaku Yakubutsu Sekkey no Kotsu (Tips for Drug Discovery Drug Molecule Design),", Elsevier Science Ltd., published on April 25, 2001, pp. 143-147 (Evidence B No. 21-1, Attachment 1)

Evidence B No. 22: Takashi Kawasuji et al., Journal of Medicinal Chemistry 2012 55 pp. 8735-8744

Evidence B No. 23: L. Haren, et al., ANUAL REVIEW OF MICROBIOLOGY 1999 Vol. 53 pp. 245-281

Evidence B No. 24: Yves Pommier et al., Advances in Virus Research 1999 Vol. 52 pp. 427-458

Evidence B No. 25: Written oath by Dr. Nouri Neamati dated August 14, 2015,

submitted in the examination procedure for opposition to European Patent Application No. 02749384.0 corresponding to Japanese Patent Application No. 2009-57635 for the Patent

Evidence B No. 26: Nouri Neamati, Expert Opinion on Investigational Drugs 2001 Vol. 10 No. 2 pp. 281-296

Evidence B No. 27: Victor I. Ovcharenko et al., Polyhedron 1997 Vol. 16 No. 8 pp. 1279-1289

Evidence B No. 28: Report of Tomoichi Yoshinaga of Shionogi Pharmaceutical Co., Ltd. (Demandee) dated July 29, 2016 (Yoshinaga Report 3)

Evidence B No. 29: Arpita Agrawal, et al., PNAS, 2012 Vol. 109 No. 7 pp. 2251-2256

Evidence B No. 30: Statement in Wikipedia for "IC50", [online] Internet <URL: https://ja.wikipedia.org/wiki/IC50>

Evidence B No. 31: He Zhao et al., Journal of Medicinal Chemistry 1997 Vol. 40 No. 8 pp. 1186-1194

Evidence B No. 32: Mario Sechi et al., Antiviral Chemistry & Chemotherapy 2005 16 pp. 41-64

Evidence B No. 33: Reveendra Dayam et al., Journal of Medicinal Chemistry 2008 Vol. 51 No. 5 pp. 1136 -1144

Evidence B No. 34: Written statement submitted by Merck (a Demandant group company) on February 12, 2015 in the examination procedure for opposition to European Patent Application No. 02749384.0 corresponding to Japanese Patent Application No. 2009-57635 for the Patent

Evidence B No. 35: Written opinion by Hiroshi Yoshida (Professor, Graduate School of Law, Hokkaido University) dated July 28, 2016

Evidence B No. 36: Judgment of 2006 (Gyo-Ke) No. 10232, pronounced on October 10, 2007

Evidence B No. 37: Guidelines for Examination in the European Patent Office (November 2015 edition), European Patent Office, Part F - Chapter III-3, Section 5.1 Only variants of the invention are incapable of being performed

Evidence B No. 38: Document entitled "Monthly Research Summary Report (April)" dated April 26, 2001 by reporters Ryuichi Kiyama and Masahiro Fuji (both are employees of the Demandee Shionogi Pharmaceutical Co., Ltd.).

Evidence B No. 39: Tomokazu Yoshinaga et al., Antimicrobial Agents and Chemotherapy 2015 Vol. 59 No. 1 pp. 397-406

Evidence B No. 40: Prescribing Information regarding TIVICAY (dolutegravir)

(revised in August 2015) prepared by ViiV Healthcare, sections of Highlights of Prescribing Information and Full Prescribing Information

Evidence B No. 41: Prescribing Information regarding ISENTRESS (raltegravir) (revised in February 2011) prepared by ViiV Healthcare, sections of Highlights of Prescribing Information and Full Prescribing Information

Evidence B No. 42: Prescribing Information regarding STRIBILD (elvitegravir) (revised in revised in August 2012) prepared by ViiV Healthcare, sections of Highlights of Prescribing Information and Full Prescribing Information

Evidence B No. 43: International Publication No. WO 01/09114

Evidence B No. 44: International Publication No. WO 01/98248

Evidence B No. 45: Article on the official homepage of the American Chemical Society entitled "Recognizing our Heroes of Chemistry", [online] Internet <URL:https://www.acs.org/content/acs/en/funding-and-awards/awards/industry/heroes.html>

Evidence B No. 46: Akiko Kawashima et al., Eur. J. Biochem. 1998 vol. 255 pp. 12-23

Evidence B No. 47: Joseph A. Ippolite et al., Int. J. Biol. Macromol. 1992 vol. 14 August pp. 193-197

Evidence B No. 48: S. M. N. Efange et al., J. Med. Chem. 1990 33 pp. 3133-3138

Evidence B No. 49: Subramaniam Ananthan et al., J. Med. Chem. 1993 36 pp. 479-490

Evidence B No. 50: Zongchao Jia et al., The Journal of Biological Chemistry 1995 vol. 270 No. 10 pp. 5527- 5533

Evidence B No. 51: Report dated October 3, 2016 entitled "Second Expert Report of Professor Youla Stratigoula Tsatrizos" prepared by Professor Tsantrizos (Faculty of Chemistry, McGill University)

Evidence B No. 52: Ralph J. Fessenden et al., Kagaku-Dojin Co., Ltd., Fundamentals of Organic Chemistry, 1st Edition, 2nd Edition, published on May 20, 1995, pp. 324-339

Evidence B No. 53: Written statement dated October 28, 2016 by Hironori Morioka, an employee of Demandee Shionogi Pharmaceutical Co., Ltd.

Evidence B No. 54: Michel Meyer et al., Journal of the American Chemical Society 1997 vol. 119 No. 42 pp. 10093-10103

Evidence B No. 55: R. E. Bowman et al., Journal of the Chemical Society 1957 pp. 1583-1588

Evidence B No. 56: National Publication of International Patent Application No. 2001-508811, the date of publication July 3, 2001

Evidence B No. 57: R. Richard Goehring et al., Journal of Medicinal Chemistry 1990 Vol. 33 No. 3 pp. 926-931

Translation of Evidence A No. 26

Translation of Evidence A No. 27

Evidence B No. 58: Koichi Shudo, Ed., Molecular Design, Hirokawa Shoten Co., Ltd., published on June 25, 1990

Evidence B No. 59: Written opinion prepared by Professor Kimachi (Professor, Department of Pharmacy, Mukogawa Women's University), prepared on April 10, 2017

Evidence B No. 60: International Publication No. WO 00/39086

Evidence B No. 61: International Publication No. WO 99/50245

Evidence B No. 62: International Publication No. WO 02/36734 (published on May 10, 2002)

Evidence B No. 63: International Publication No. WO 02/30930 (published on April 18, 2002)

Evidence B No. 64: International Publication No. WO 01/17968 (published on March 15, 2001)

Evidence B No. 65: Chem. Rev. 1996 96 pp. 3147 -3176

Evidence B No. 66: International Publication No. WO 99/62513

Evidence B No. 67: International Publication No. WO 01/00578 (published on January 4, 2001)

Evidence B No. 68: International Publication No. WO 02/30931 (published on April 18, 2002)

No. 6. Judgment

1. Regarding Reason for Invalidation 1

Since the Patent Invention is the invention of a pharmaceutical composition as stated above, it is the invention of a product stipulated in Article 2(3)(i) of the Patent Act. In addition, working of the invention of a product includes the action of using the product. In view of the statement in (b) of the Patent Specification, which will be stated later, the use of the product in the Patent Invention means that the above pharmaceutical composition is administered to a patient infected with a virus such as HIV to exert an integrase inhibitory activity on the patient and bring about a

pharmacological action of preventing and treating various diseases caused by viruses. Then, in general, considering that it is difficult to predict from the chemical structure of a compound what kind of pharmacological action the compound exerts and what kind of medicine it is useful for, in order to be able to say that the statements in the Detailed Description of the Invention of the Patent Specification are clear and sufficient to the extent that a person skilled in the art could carry out the Patent Invention, it is necessary to include a description sufficient for a person skilled in the art to recognize that the pharmaceutical composition exerts the pharmacological activity in addition to the view of the inventor of the Patent Invention that the pharmaceutical composition brings about the pharmacological activity on the patient as well as the dosage, administration method, and formulation method required for administering the pharmaceutical composition to the patient.

Then, we will examine the statements in the Detailed Description of the Patent Invention of the Patent Specification. With respect to administering the pharmaceutical composition to the patient and exerting an integrase inhibitory activity on the patient to bring about a pharmacological action of preventing and treating various diseases caused by viruses, the Detailed Description of the Invention includes the following description (a) to (d).

Note that, the pages and lines are those in the corresponding Patent Gazette.

(A: page 2, line 32 to page 5, line 19)
"[Technical Field]
[0001]
Technical Field

The present invention relates to an antiviral agent, especially, a compound having an α-hydroxy-α, β unsaturated ketone as a partial structure, and a pharmaceutical composition as an integrase inhibitor containing the same.

[Background Art]
[0002]
Background Art

Among viruses, human immunodeficiency virus (HIV), a kind of retrovirus, is known to cause acquired immunodeficiency syndrome (AIDS). The therapeutic agent for AIDS is mainly selected from the group of reverse transcriptase inhibitors (e.g., AZT, 3TC) and protease inhibitors (e.g., Indinavir), but they are proved to be accompanied by side effects such as nephropathy and the emergence of resistant viruses.

Thus, the development of anti-HIV agents having the other mechanism of action has been desired.

Examples of the integrase inhibitor include 1,3-dioxobutanoic acids and 1,3-propanediones stated in WO99/50245, WO99/62520, WO99/62897, WO99/62513, WO00/39086, and WO01/00578. Another integrase inhibitor is acrylic acid derivative stated in WO01/17968.

The other recently reported types are aza- or polyazanaphthalenylcarboamide derivative stated in WO2002/30426, WO2002/30930, WO2002/30931, and WO2002/36734.

A compound having a similar structure to the present invention compound is N-substituted-3-carboamide-4-hydroxy-5-oxo-3-pyrroline derivative with an anti-inflammatory effect stated in Eur. J. Med. Chemical-Chim. Ther. (1979), 14(2), 189-190. Pharmazie (1997), 52(4), 276-278 discloses 1-methyl-4-arylcarbamido-2,3-dioxopyrrolidine derivative as an intermediate. WO92/06954 discloses pyrolizinedione derivative with an inhibitory effect on aldose reductase. J. Med. Chemical (1976), 19(1), 172-173 discloses N-substituted-4,5-dioxopyrrolidine-3-carboxyanilide derivative with anti-inflammatory effect.

Furthermore, Journal of Physical Chemistry A (2002), 106(11), 2497-2504 discloses pyrimidine derivative without mentioning any pharmaceutical use.

On the other hand, T'ai-wan K'o Hsueh (1997), 31(3-4), 130-135 discloses 3-hydroxy-7-(phenylmethoxy)-2-(2-quinolinyl)-4H-1-benzopyrane-4-one. Examples of a compound having a structure of "4H-1-benzopyrane-4-one" include flavonoid derivative with anti-HIV activity stated in

[1] J. Nat. Prod. (2001), 64(4), 546-548,

[2] Anticancer Res. (2000), 20(4), 2525-2536,

[3] WO98/11889, and

[4] Pharmazie (1998), 53(8), 512-517, although the action of mechanism is not mentioned therein.

[Summary of Invention]

[Problem to be solved by the invention]

[0003]

Under the above circumstance, the development of a novel integrase inhibitor has been desired.

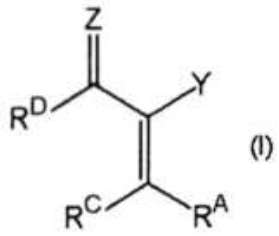
[Means for solving the problem]

[0004]

The present inventors have intensively studied to find a novel antiviral agent, the

following compound (I), its prodrug, or a pharmaceutically acceptable salt or solvate thereof, possessing an integrase inhibitory activity;

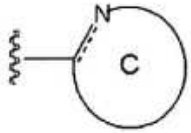
[Chemical Formula 1]



(I)

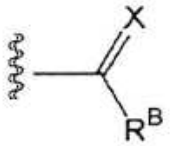
(wherein R^C and R^D taken together with the neighboring carbon atoms form a ring, and the ring may be a condensed ring; Y is hydroxy, mercapto, or amino; Z is O, S or NH; R^A is shown by

[Chemical Formula 2]



(wherein C ring is an N-containing aromatic heterocycle, wherein at least one atom neighboring to the atom at the bonding-position is an N atom; the broken line shows the presence or absence of a bond) or by

[Chemical Formula 3]



(wherein X is O, S or NH; R^B is a substituent selected from substituent group A);

at least one of the ring formed by R^C and R^D, C ring or R^B is substituted with a group of-Z^1-Z^2-Z^3-R^1 (wherein Z^1 and Z^3 are each independently a bond, an optionally substituted alkylene or an optionally substituted alkenylene; Z^2 is a bond, an optionally substituted alkylene, an 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 alkyl, 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); and

the ring formed by R^C and R^D, C ring or R^B is optionally substituted with a non-interfering substituent at any position except where the group of-Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above) locates;

[0005]

Substituent group A: 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, sulfoamino, formyl, alkylcarbonyl, alkylcarbonyloxy, hydrazino, morpholino, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroaryl alkyl, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted aryl thio, optionally substituted heteroarylthio, optionally substituted aralkyloxy, optionally substituted heteroarylalkyloxy, optionally substituted aralkylthio, optionally substituted hetero aryl alkyl thio, optionally substituted aryloxy alkyl, optionally substituted heteroaryloxyalkyl, optionally substituted arylthio alkyl, optionally substituted hetero arylthio alkyl, optionally substituted aryl sulfonyl, optionally substituted heteroarylsulfonyl, optionally substituted aralkylsulfonyl and optionally substituted heteroarylalkylsulfonyl) (hereafter referred to as 'the present invention compound').

The present inventors further found that the present invention compound and a pharmaceutical composition containing the same are useful as an antivirus agent, anti-retrovirus agent, anti-HIV agent, anti-HTLV-1 (Human T cell leukemia virus type 1) agent, anti-FIV (Feline immunodeficiency virus) agent, and anti-SIV (Simian immunodeficiency virus) agent, esp., anti-HIV agent and an integrase inhibitor, thereby achieving the present invention.

The present invention provides the present invention compound, its prodrug, a pharmaceutically acceptable salt or solvate thereof, a pharmaceutical composition containing the same as an active ingredient, an antivirus agent, an anti-HIV agent, an integrase inhibitor, and an anti-HIV mixture. These are useful as an anti-HIV agent as well as an anti-AIDS agent for diseases such as AIDS, its related clinical syndrome, e.g., AIDS related complication (ARC), persistent generalized lymphadenopathy (PGL), Kaposi sarcoma, pneumocystis carini pneumonia, sudden thrombocy topenic purpura, AIDS related neurological symptom, for example, AIDS dementia complications AIDS-associated encephalopathy multiple sclerosis or tropical spastic paraphrases, and anti-HIV antibody positive and HIV positive symptom in asymptomatic patients."

(B: Page 90, line 46 to page 92, line 8)
"[0034]

Use of the present invention compounds is explained below.

The present invention compound is useful for preparing a pharmaceutical composition such as antivirus agent. The present invention compound, possessing a remarkable inhibitory activity on integrase of virus, is expected to exhibit a preventing or treating effect for diseases caused by viruses which grow at least via production of integrase in infected animal cells, thus being useful as an integrase inhibitor against a retro-virus (e.g., HIV-1, HIV-2, HTLV-1, SIV, FIV) as well as an anti-HIV agent.

Further, the present invention compound can be used in combination with other anti-HIV agents having a different action of mechanism such as a reverse transcriptase inhibitor and/or a protease inhibitor. Since none of the integrase inhibitors has been available for sale, a combination therapy of the present invention compound with a reverse transcriptase inhibitor and/or a protease inhibitor is very useful.

Further, the present invention compound can be used as a combined agent for enhancing the anti-HIV activity of other anti-HIV agents, as shown in the cocktail therapy.

Further, the present invention compound can be used in gene therapy in order to prevent a retrovirus vector derived from HIV or MLV from spreading over non-targeted tissues. In particular, in a case that cells infected with a vector in vitro is put back to a body, administration of the present invention compound in advance can prevent an unnecessary infection in the body.

The compounds of the present invention can be administered orally or parenterally. For oral administration, the compounds of the present invention can be used in any form of usual formulations, for example, solid formulations such as tablets, powders, granules, capsules; aqueous formulations; oleaginous suspensions; and solutions such as syrup or elixir. For parenteral administration, the compounds of the present invention can be used as an aqueous or oleaginous suspension injection, or nose drops. In the preparation of such formulations, conventional excipients, binding agents, lubricants, aqueous solvents, oleaginous solvents, emulsifying agents, suspending agents, preservatives, stabilizers, and the like can be optionally used. Preferred is an oral agent as an HIV-agent.

A formulation according to the present invention may be manufactured by combining (for example, admixing) a curatively effective amount of a compound of the present invention with a pharmaceutically acceptable carrier or diluent. The formulation

of the present invention may be manufactured with well-known and easily available ingredients in accordance with a known method.

In the case of manufacturing a pharmaceutical composition according to the present invention, an active ingredient is admixed or diluted with a carrier, or they are contained in a carrier in the form of capsule, sacheier, paper, or another container. In the case of functioning a carrier as a diluent, the carrier is a solid, semi-solid, or liquid material which functions as a medium. Accordingly, a formulation according to the present invention may be produced in the form of tablet, pill, powder medicine, intraoral medicine, elixir agent, suspending agent, emulsifier, dissolving agent, syrup agent, aerosol agent (solid in liquid medium), and ointment. Such a formulation may contain up to 10% of an active compound. It is preferred to formulate a compound of the present invention prior to administration.

Any suitable carrier well known to those skilled in the art may be used for the formulation. In such formulation, a carrier is in the form of solid, liquid, or a mixture of solid and liquid. For instance, a compound of the present invention is dissolved into 4% dextrose/0.5% sodium citrate aqueous solution so as to be 2 mg/ml concentration for intravenous injection. Solid formulation includes powder, tablet, and capsule. Solid carrier consists of one or more of material(s) for serving also as fragrance, lubricant, dissolving agent, suspension, binder, tablet disintegrator, or capsule. A tablet for oral administration contains a suitable excipient such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, and the like together with a disintegrator such as corn starch, alginic acid and the like and/or a binder such as gelatin, acacia, and the like, and a lubricant such as magnesium stearate, stearic acid, talc, and the like.

In a powder medicine, a carrier is a finely pulverized solid which is blended with finely pulverized active ingredients. In a tablet, active ingredients are admixed with a carrier having required binding power in a suitable ratio, and it is solidified in a desired shape and size. Powder medicine and tablet contain about 1 to about 99% by weight of the active ingredients being novel compounds according to the present invention. Examples of suitable solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth gum, methyl cellulose, sodium carboxymethylcellulose, low-melting wax, and cocoa butter.

A liquid formulation includes suspending agent, emulsifier, syrup agent, and elixir agent. Active ingredients may be dissolved or suspended into a pharmaceutically acceptable carrier such as sterile water, a sterile organic solvent, a mixture thereof, and the like. Active ingredients may be dissolved frequently into a suitable organic solvent such as propylene glycol aqueous solution. When finely pulverized active ingredients

are dispersed into aqueous starch, sodium carboxyl methylcellulose solution, or suitable oil, the other compositions can be prepared.

Although an appropriate dosage of the compound of the present invention varies depending on the administration route, age, body weight, conditions of the patient, and kind of disease, in the case of oral administration, the daily dosage can be between approximately 0.05-3000 mg, preferably approximately 0.1-1000 mg, for an adult. The daily dosage can be administered in divisions. In the case of parenteral administration, the daily dosage for an adult can be between approximately 0.01-1000 mg, preferably approximately 0.05-500 mg."

(C: page 348, line 5 to page 349, line 29)
"[0036]
Experimental Example

The inhibitory activities against integrase of the compounds in the present invention have been determined by the assay described below.

(1) Preparation of DNA Solutions.

Substrate DNA and target DNA, which sequences were indicated below, were synthesized by Amersham Pharmacia Biotech and dissolved in KTE buffer (composition: 100 mM KCl, 1 mM EDTA, 10 mM Tris-HCl (pH 7.6)) at concentration of 2 pmol/μl and 5 pmol/μl, respectively. The DNA solutions were annealed with each complement by slowly cooling after heating.

(Substrate DNA sequences)

5'- Biotin-ACC CTT TTA GTC AGT GTG GAA AAT CTC TAG CAG T-3'

3'- GAA AAT CAG TCA CAC CTT TTA GAG ATC GTC A-5'

(Target DNA sequences)

5'- TGA CCA AGG GCT AAT TCA CT-Dig-3'

3'-Dig-ACT GGT TCC CGA TTA AGT GA -5'

(2) Calculations of the Percent Inhibitions (the IC_{50} Values)

Streptavidin, obtained from Vector Laboratories, was dissolved in 0.1 M carbonate buffer (composition: 90 mM Na_2CO_3, 10 mM $NaHCO_3$) at a concentration of 40 μg/ml. After coating each well of microtiter plates (obtained from NUNC) with 50 μl of the above solution at 4°C. overnight, each well was washed twice with PBS (composition: 13.7 mM NaCl, 0.27 mM KCl, 0.43 mM Na_2HPO_4, 0.14 mM KH_2PO_4) and blocked with 300 μl of 1% skim milk in PBS for 30 min. Additionally, each well was washed twice with PBS, followed by addition of 50 μl of substrate DNA solution (0.04 pmol/μl) diluted to one-fiftieth with NTE buffer (composition: 1M NaCl, 10 mM

Tris-HCl (pH8.0), 1 mM EDTA). The microtiter plates were kept under shaking at room temperature for 30 min. Then, each well was washed twice with PBS and once with distilled H_2O.

Subsequently, in each well prepared above were added 45 μl of the reaction buffer prepared from 12 μl of the buffer (composition: 150 mM MOPS (pH 7.2), 75 mM $MnCl_2$, 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin-fraction V), 1 μl of target DNA (5 pmol/μl), and 32 μl of the distilled water. Additionally, 6 μl of either a test compound in DMSO or DMSO for positive control (PC) was mixed with the above reaction buffer, then 9 μl of an integrase solution (30 pmol/μl) was added and mixed well. In the well of negative control (NC) was added 9 μl of the integrase dilution buffer (composition: Hepes (pH7.6), 400 mM potassium glutamate, 1 mM EDTA, 0.1% NP-40, 20% glycerol, 1 mM DTT; 4 M urea).

The microtiter plates were incubated at 30°C for 1 hour. The reaction solution was removed and each well was washed twice with PBS. Subsequently, each well of the microtiter plates was filled with 100 μl of anti-digoxigenin antibody labeled with alkaline phosphatase (Sheep Fab fragment: obtained from Boehringer) and incubated at 30°C for 1 hour. Then, each well was washed twice with 0.05% Tween 20 in PBS and once with PBS. Next, 150 μl of the Alkaline phosphatase reaction buffer (composition: 10 mM p-Nitrophenylphosphate (obtained from Vector Laboratories), 5 mM $MgCl_2$, 100 mM NaCl, 100 mM Tris-HCl (pH 9.5)) was added in each well. The microtiter plates were incubated at 30°C for 2 hours. The optical density (OD) at 405 nm of each well was measured and the percent inhibition was determined by the following expression.

Percent inhibition (%)=100[1-{(C abs.-NC abs.)/(PC abs.-NC abs.)}]

C abs.; the OD of the well of the compound

NC abs.: the OD of the negative control (NC)

PC abs.: the OD of the positive control (PC)

Next, the IC_{50} value is calculated by the following formula using the above percent inhibition.

When the percent inhibition (%) is X% at the concentration of x μg/ml and the percent inhibition (%) is Y% at the concentration of y μg/ml, one of which is more than 50% and the other is less than 50%, IC_{50} can be determined by the following expression.

IC_{50} (μg/ml) = x - {(X - 50)(x - y)/(X - Y)}

The IC_{50} values, the concentration of the compounds at percent inhibition 50%, are shown in the following Table 1. Compound No. in the Table 1 is the same as

compound No. of the above example.

[TABLE 1]

化合物 No.	IC_{50} (μg/ml)	化合物 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		

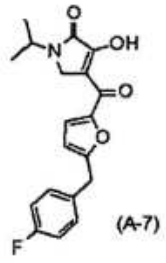
化合物 No. compound No.

The compounds of the present invention except the above compounds had the same or higher integrase inhibitory activities.

Moreover, the compounds of the present invention have high stability against metabolism and they are superior inhibitory agents against integrase.

(D: Page lines, etc. are displayed for each description)

"

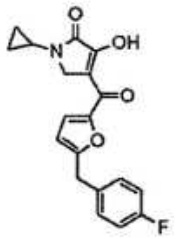


(A-7)

" (page 92)

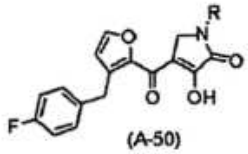
"(A-12-a) 4-[3-(4-Fluorobenzyl)benzoyl]-3-hydroxy-1-methyl-1,5-dihydropyrrole-2-one (page 95, lines 30 to 31)

"



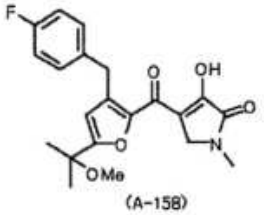
(A-17)

" (page 96)
"(A-17-c) 1-Butyl-4-[5-(4-fluorobenzyl)furan-2-carbonyl]-3-hydroxy-1,5-dihydropyrrole-2-one" (page 98, lines 41 to 42)
"



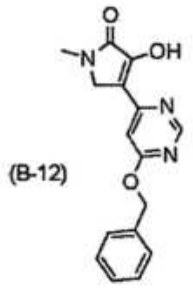
(A-50)

" (page 108)
"(A-141-k) 4-[5-(4-Fluoro-2-isopropoxybenzyl)furan-2-carbonyl]-3-hydroxy-1-methyl-1,5-dihydropyrrole-2-one" (page 140, lines 43 to 44)
"



(A-158)

" (page 145)
"(B-6-a) 3-Hydroxy-1-methyl-4-(6-phenethylpyrimidine-4-yl)-1,5-dihydropyrrole-2-one" (page 156, lines 13 to 14)
"(B-6-d) 1-Cyclohexyl-3-hydroxy-4-(6-phenethylpyrimidine-4-yl)-1,5-dihydropyrrole-2-one" (page 156, lines 37 to 38)
"

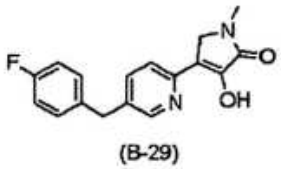


(B-12)

"(page 158)

"(B-12-b) 4-[6-(4-Fluorobenzyloxy)pyrimidine-4-yl]-3-hydroxy-1-methyl-1,5-dihydropyrrole-2-one" (page 159, lines 32 to 33)

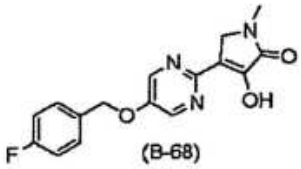
"



(B-29)

"(page 167)

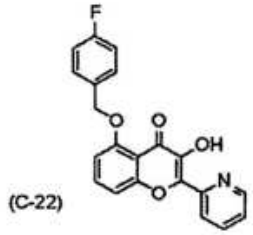
"



(B-68)

" (page 180)

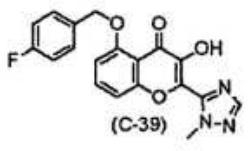
"



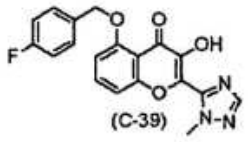
(C-22)

" (page 198)

"

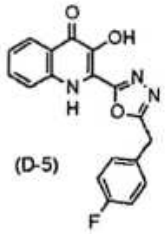


" (page 200)



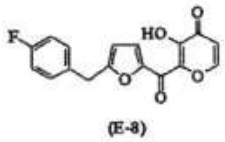
" (page 204)

"



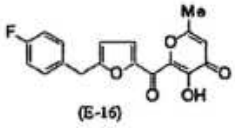
" (page 215)

"



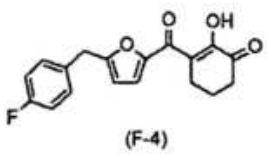
" (page 218)

"



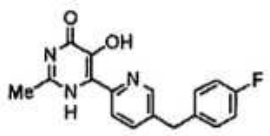
" (page 220)

"



" (page 233)

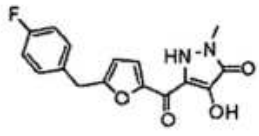
"



(G-7)

" (page 234)

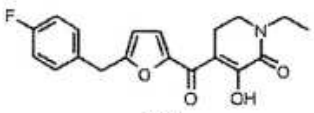
"



(H-7)

" (page 236)

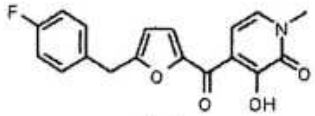
"



(I-4)

" (page 239)

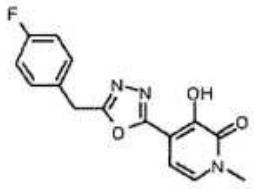
"



(J-4)

" (page 241)

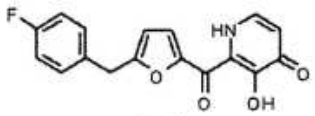
"



K-4

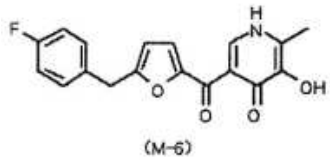
" (page 243)

"



(L-4)

" (page 244)
"



(M-6)

" (page 246)

(2) Examination

The Detailed Description of the Invention of the Patent Specification states that, according to the description of the above (a), the inventor's view of the Patent Invention that the compound represented by the formula (I) described in (a) was found to be useful as an integrase inhibitor; according to the description in the above (b), the dose, administration method, and formulation method required for administering the pharmaceutical composition to the patient; according to the description of the above (c), a pharmacological test method for assaying an integrase inhibitory action; and similarly according to the description in [Table 1] of the above (c) e, the value of IC_{50} showing an integrase inhibitory action for the compounds Nos. A-7 to M-6. However, according to the description of the above (d), these compounds are different from the compounds represented by the formula (I) of the Patent Invention in terms of their chemical structures. The pharmacological data of the compounds Nos. A-7 to M-6 are those of 27 compounds according to the description in [Table 1] of the above (c). In view of the description of the above (d), all of these compounds are limited to a few groups, such as the group $-Z^1-Z^2-Z^3-R^1$ is 4-fluorobenzyl group, of the compounds represented by the formula (1) represented in the above (a) of the Patent Specification, and are also limited to those having a very small number of groups in the substituent A. Therefore, from the pharmacological data of these compounds, it cannot be said that the integrase inhibitory effects of compounds represented by formula (I) represented in the above (a), which can be said to include a wide variety of compounds, have been clarified. It cannot be said that the integrase inhibitory action of the compound of the Patent Invention, which is a part thereof, has been clarified.

In addition, even if there is no disclosure about the pharmacological test results such that the fact that the above pharmaceutical composition exerts the above pharmacological action belonged to the common general technical knowledge at the

time of filing application for the Patent Invention, it cannot be said that a person skilled in the art could recognize that the above pharmaceutical composition exerts the above pharmacological action.

Then, it cannot be said that the Detailed Description of the Invention of the Patent Specification is sufficient for a person skilled in the art to recognize that the pharmaceutical composition of the Patent Invention exerts the above pharmacological action.

Next, the Demandee's allegation will be examined.

The common general technical knowledge that existed at the time of filing application for the Patent is, for example, that a chelator-type inhibitor had been a promising candidate as an integrase inhibitor. After all, taking into consideration the common general technical knowledge, (Allegation 1) to (Allegation 9), (Allegation 11) to (Allegation 16), (Allegation 18) to (Allegation 19), and (Allegation 21-4) can be understood as follows: It would be apparent to a person skilled in the art that the Patent Invention compound is a 2-nuclear cross-linked tridentate ligand type inhibitor that inhibits integrase activity, and thus unlikely shows no integrase inhibitory activity at all. From the abundant pharmacological data represented in the Patent Specification, the person skilled in the art could understand that the compound of the Patent Invention has an integrase inhibitory activity.

However, according to Evidence B Nos. 1-1 to 16, which are alleged to be the evidence of the existence of the common general technical knowledge, Evidence B No. 1-1 is the opinion of one expert. Thus, it cannot be immediately said from this view that the common general technical knowledge existed at the time of filing application for the Patent Invention. In addition, Evidence B No. 1-2 is not directly related to the existence of the common general technical knowledge at the time of filing application for the Patent Invention. Evidence B Nos. 1-3 to 16 are academic treatises or patent gazettes intended to disclose the state-of-the-art technology at the time of publication. Although it can be said that the matters stated in the documents were publicly known at the time of filing application for the Patent Invention, it cannot be said that the matters were common general technical knowledge at the time of filing application for the Patent Invention.

Furthermore, it can be understood that the figure corresponding to the "model" in the allegation of "a structure, which can function as a tridentate ligand that chelates to two metal ions in Compound 1 of the Corrected Invention, is essential as one being coincident with the model stated in review articles and the like" is Figure 14.3

represented in Evidence B No. 24. (Evidence B No. 23 and No. 24 do not contain any other relevant figures.)

Then, Figure 14.3 is as follows:

"

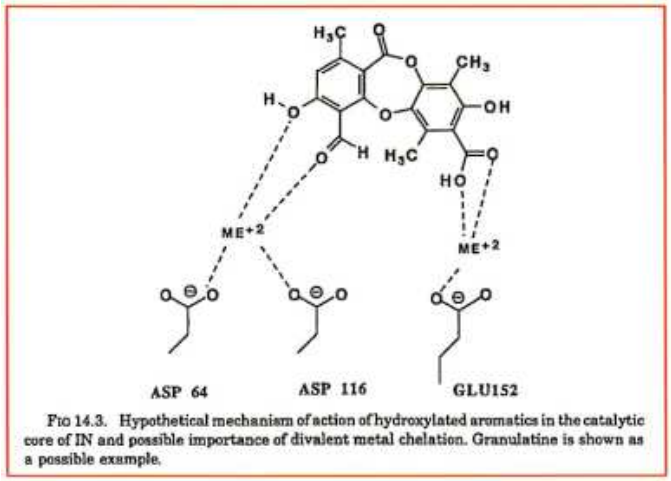


FIG 14.3. Hypothetical mechanism of action of hydroxylated aromatics in the catalytic core of IN and possible importance of divalent metal chelation. Granulatine is shown as a possible example.

"

"It is accompanied by the description of "Hypothetical mechanism of action of hydroxylated aromatics in the catalytic core of IN and possible importance of divalent metal chelation. Granulaine is shown as a possible example." A hydroxylated aromatic compound having a structure in which two benzene rings on the left and right are bonded via a 7-membered ring in the center, and two divalent metals represented as "ME^{2+}" are illustrated. The divalent metal on the left side is chelated by forming a hydrogen bond with a hydroxy group and a carboxyl group bonded to the benzene ring on the left side, and the divalent metal on the right side is bonded to the benzene ring on the right side and chelated by forming a hydrogen bond with two oxygens that make up the carboxyl group.

Then, the hydroxylated aromatic compound in this figure is a compound having two portions (one on each of the left and right benzene rings) that function as a mononuclear bidentate type ligand in one molecule (tentatively, it is called a '1-nucleus 2-locus * 2 type ligand'), but not a ligand in the type of 2-nuclear cross-linked hydroxylate ligand. Therefore, the Demandee's allegation is deemed to be based on an erroneous understanding of the statements in Evidence B Nos. 23 and 24 and cannot be adopted.

Therefore, the allegation of the Demandee discussed above cannot be accepted.

In addition, (Allegation 21-1) to (Allegation 21-3) and (Allegation 21-5) are understood to assert that the compounds represented by Chemical formula (I) recited in Patent Invention 1 of the Patent include a compound having, at first glance, a chemical structure similar to 27 compounds whose pharmacological data are represented in the description of the Patent and a compound satisfying the items (a) to (d) that can be recognized from the 27 compounds, but not a compound listed in Evidence A No. 10, which the Demandant alleged to be inactive. The difference in chemical structure from the 27 compounds is equivalent as a so-called bioisostare. Therefore, 27 compounds are equivalent to the compound represented by Chemical formula (I) recited in Patent Invention 1.

However, in general, even compounds having very high chemical structural resemblance may not have similar specific properties or physical properties at all. Further, it is common general technical knowledge in the art that this point is the same in the technical field of the integrase inhibitor recited in the Patent Invention. Taking these matters into consideration, even if the chemical structure of the compound represented by Chemical formula (I) recited in Patent Invention 1 is at first glance similar to 27 compounds whose pharmacological data are represented in the description of the Patent, it cannot be immediately understood that the compound represented by chemical formula (I) recited in Patent Invention 1 is an integrase inhibitor.

In fact, the compounds that satisfy the matters (a) to (d) that can be recognized from the 27 compounds include Merck #11 (compound having no integrase inhibitory activity) stated in Evidence A No. 10, and this fact is consistent with the above consideration.

Furthermore, [Allegation 21-5] based on Evidence B No. 65 cannot be accepted, because of the following reasons.

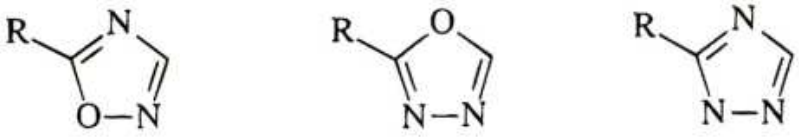
Specifically, the wording "amide and 1,3,4-oxadiazole are equivalent as so-called bioisostares" in the statement of the Demandee is understood to mean that "the amide bond (-NHCO-) and the 1,3,4-oxadiazole bond (divalent linking group obtained by removing two hydrogens from 1,3,4-oxadiazole) are so-called bioisostares."

On the other hand, the matters pointed out by the Demandee in Evidence B No. 65 are as follows:

"4. Amide Group Bioisosteres

... Heterocyclic rings such as 1,2,4-oxadiazoles (92),[164-168] 1,3,4- oxadiazoles (93),[169-171] 1,2,4-triazoles (94), and [172] (Figure 76), have also been used as replacements for amide

or ester bonds.



92 93 94

図76

図 76 Figure 76

"(Partial translation of Evidence B No. 65)
In light of these chemical structural formulas, it is understood that the 1,3,4-oxadiazole referred to here is not a divalent linking group, but a monovalent cyclic group at the end of the compound (in each chemical structural formula shown in the above figure, 'R' is removed) but the substitute of the terminal amide group (R-$CONH_2$) or ester group (R-COOR') of the compound. Then, the above quoted part does not contain what Demandee alleges to be contained.

Rather, after the pointed out part, the following table entitled 'Table 48. Bioisosteres of the Amide Bond' is represented.
"

Table 48. Bioisosteres of the Amide Bond

bioisostere	formula
amide	−NHCO−
reversed amide	−CONH−
thioamide	−NHCS−
amide homologue	$-CH_2NHCO-$
ketomethylene	$-COCH_2-$
urea	−NHCONH−
methyleneamino	$-CH_2NH-$
carbamate	$-NHCO_2-$
thiocarbamate	−NHCOS−
ester	$-CO_2-$
sulfonamide	$-NHSO_2-$
hydroxyethylene	$-CH(OH)CH_2-$

"

Specific examples of amide-bonded bioisostars listed in the table include "Amide (-NHCO-)", "reversed amide (-CONH-)", and "thioamide (-NHCS-)." However, the table does not list 1,3,4-oxadiazole bonds.

Then, (Allegation 21-5) is based on a misunderstanding of Evidence B No. 65, and cannot be adopted in this respect either.

The part (section) pointed out by the Demandee is included in the chapter entitled "B. Nonclassical Bioisosteric Replacements of Functional Groups" (page 3165). Following the above title, the paragraph beginning with "In this section" states as follows: "As can be the case for any bioisostere, not all of these replacements will necessarily result in a compound with comparable biological activity to the template drug."

Then, even if there is a statement that it is "amide and 1,3,4-oxadiazole are equivalent as so-called bioisostars" in Evidence B No. 65, the statement is premised on "not all of these replacements will necessarily result in a compound with comparable biological activity to the template drug." Therefore, it cannot be said that the compound represented by the chemical formula (I) recited in Patent Invention 1 and the 27 compounds are equivalent.

Even if the above common general technical knowledge existed at the time of filing application for the Patent Invention, it cannot be said that it allowed a person skilled in the art to clearly understand that the compounds of the Patent Invention not listed in each of the above Evidence B is hardly imagined to be a binuclear tridentate ligand type inhibitor that inhibits integrase activity and to show no integrase inhibitory activity. As explained above, it cannot be said that the integrase inhibitory action of the compound of the Patent Invention has been clarified from the pharmacological data represented in the Patent Specification.

Therefore, all of the above allegations made by the Demandee are groundless.

After all, taking into consideration the pharmacological data represented in the Patent Specification, (Allegation 10) and (Allegation 14) as well as (Allegation 20) and (Allegation 21) can be understood as follows: A person skilled in the art could understand that the Patent Invention compound and the Patent compound have integrase inhibitory activities. Therefore, it is understood that the pharmacological data represented in Evidence B Nos. 8, 9, 10, and 28 submitted after filing application for the Patent Invention should be taken into consideration.

However, no disclosure about the above pharmacological data is found in the Patent Specification at all. Submitting such data after filling application for the Patent to allow the statements in the Detailed Description of the Invention of the Patent Specification to comply with the requirements as provided in Article 36(4)(i) of the Patent Act should not be allowed in light of the purpose of Japan's patent system, which

adopts the so-called first-to-file principle. Even if it exists, it cannot be said that those skilled in the art could understand that the compound of the Patent Invention has an integrase inhibitory activity, as explained above. Therefore, the above Demandee's allegations lack premises.

Therefore, the above pharmacological data cannot be taken into consideration, and the Demandee's (Allegation 10) and (Allegation 14) as well as (Allegation 20) and (Allegation 21) cannot be adopted.

Therefore, it cannot be said that the statements in the Detailed Description of the Invention of the Patent Specification are stated in such a manner sufficiently clear and complete to be carried out by a person skilled in the art.

As stated above, therefore, the application for the Patent Invention does not meet the requirements stipulated in Article 36(4)(i) of the Patent Act for the statements in the Detailed Description of the Invention.

2. Regarding Reasons for Invalidation 2

Whether or not the statements in the scope of claims conform to the requirements stipulated in Article 36(6)(i) of the Patent Act, the so-called support requirement of the description, should be judged by considering the following: The recitation in the scope of claims are compared with the description in the Detailed Description of the Invention to determine whether or not the invention recited in the scope of claims is the invention described in the Detailed Description of the Invention and is within the range that a person skilled in the art could solve the problems of the Patent Invention in view of the common general technical knowledge at the time of filing application of the Patent even if there is no statement or suggestion in the Detailed Description of the Invention. It is reasonable to understand that the existence of the support requirements of the Patent Specification is the burden of proof of the applicant for the Patent, the Demandee.

Here, the Patent Invention is an invention of a pharmaceutical composition of an integrase inhibitor as stated above. The problem is nothing but to bring about a pharmacological action of exerting an integrase inhibitory action on a patient infected with a virus to prevent and treat various diseases caused by the virus.

As explained in " Regarding Reason for Invalidation 1," it cannot be said that the Detailed Description of the Invention of the Patent Specification is sufficient for a

person skilled in the art to recognize that the pharmaceutical composition of the Patent Invention exerts the above pharmacological action. In addition, even if there is no disclosure about the pharmacological test results such that the fact that the above pharmaceutical composition exerts the above pharmacological action belonged to the common general technical knowledge at the time of filing application for the Patent Invention, it cannot be said that a person skilled in the art could recognize that the above pharmaceutical composition exerts the above pharmacological action.

There is no choice but to assume that there is no recognizable range to the extent that a person skilled in the art could recognize that the problems of the Patent Invention can be solved by the statements in the Detailed Description of the Invention of the Patent Specification or to the extent that a person skilled in the art could recognize that the problem of the Patent invention can be solved in light of the common general technical knowledge at the time of filling application for the Patent without the statement or suggestion. Nevertheless, the Patent Invention is recited in the claims of the Patent Specification. Therefore, the recitation in claims of the Patent Specification do not meet the support requirements for the description.

As stated above, the application for the Patent Invention does not meet the requirements stipulated in Article 36(6)(i) of the Patent Act for the statements in the scope of claims.

3. Regarding Reasons for Invalidation 3

The Patent Invention is as stated in the above "No. 3. The Patent Invention." In addition, the Patent Invention is included in the case where "R^A" is "[Chemical Formula 3]" in "Formula (I)" in the scope of claims originally attached to the application of Japanese Patent Application No. 2001-245071 ((filed on August 10, 2001) as a basis of claiming priority (see Evidence A No. 11). Specifically, it corresponds the case that, in "[Chemical Formula 3]," X is an oxygen atom, R^B is substituted with a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$, and R^B is "optionally substituted amino," which a substituent selected from substituent group A.

Then, a priority claim for the application of the Patent Invention based on the above Japanese Patent Application No. 2001-245071 is admitted and the priority date is August 10, 2001.

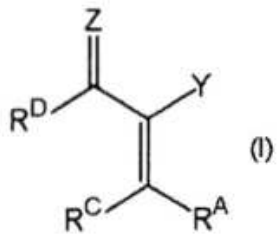
In contrast, the patent application pertaining to Evidence A No. 3 is an application claiming the priority on October 26, 2001 and thus does not fall under the earlier application stipulated in Article 29-2 of the Patent Act against the application for the Patent.

Therefore, the patent of the Patent Invention cannot be invalidated by Reasons for Invalidation 3.

4. Regarding Reasons for Invalidation 4

According to Evidence A Nos. 4 and No. 5, the content of the amendment by the written amendment submitted on April 3, 2012 in the application for the Patent Invention (hereinafter, referred to "the amendment") ["the Amendment"]) is as follows:

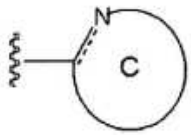
"[Claim 1]
A compound represented by the following formula (I):
[Chemical Formula 1]



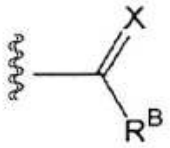
(I)

(wherein R^C and R^D taken together with the neighboring carbon atoms form a 5- to 6-membered ring containing (a) heteroatom(s), and the ring may be a condensed ring with a benzene ring;
Y is hydroxy; Z is an oxygen atom;

R^A is a group represented by the formula:
[Chemical Formula 2]



(wherein C ring is 5- or 6-membered N-containing aromatic heterocycle, wherein at least one atom neighboring to the atom at the bonding-position is a non-substituted N atom; the broken line shows the presence or absence of a bond) or a group represented by the formula:
[Chemical Formula 3]



wherein X is O; R^B is substituent group A (: substituent selected from alkyl, hydroxy, alkoxy, amino, aryl, heteroaryl, cycloalkyl, cycloalkenyl, and heterocycle);

C ring and R^B is substituted with a group of the formula: Z^1-Z^2-Z^3 -R^1 (wherein Z^1 and Z^3 are each independently a bond or an optionally substituted alkylene; Z^2 is a bond, -S-, -SO-, -SO_2-, -SO_2NH-, -$NHSO_2$-, -O-,-NH-,-NHCO-, or -CONH-); R^1 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, or optionally substituted heterocycle);

the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above); and
the C ring, R^B, or a ring formed by R^C and R^D is optionally substituted with a non-interfering substituent selected from hydrogen, halogen, alkoxycarbonyl, carboxy, alkyl, alkoxy, alkoxyalkyl, nitro, hydroxy, hydroxyalkyl, alkenyl, alkyne, alkylsulfonyl, optionally substituted amino, alkylthio, alkylthioalkyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycle, oxo, chioxo, nitroso, azide, amidino, guanidine, cyano, isocyano, mercapto, optionally substituted carbamoyl, sulfamoyl, sulfamino, holmil, alkylcarbonyl, alkylcarbonyloxy, hydrazino, morpholine, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkill, optionally substituted heteroarylalkyl, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted arylthio, optionally substituted heteroarylthio, optionally substituted aralkiroxy, optionally substituted heteroarylalkyloxy, optionally substituted aralkircio, optionally substituted heteroarylalkylthio, optionally substituted aryloxyalkyl, optionally substituted heteroaryloxyalkyl, optionally substituted arylthioalkyl, optionally substituted heteroarylthioalkyl, optionally substituted arylsulfonyl, optionally substituted heteroarylsulfonyl, optionally substituted aralkyl sulfonyl, and optionally substituted heteroarylalkyl sulfonyl, 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 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)),

a pharmaceutically acceptable salt thereof, or a solvated form thereof.

[Claim 2]

A compound, a pharmaceutically acceptable salt thereof, or a solvated form thereof of Claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing (a) heteroatom(s).

[Claim 3]

A compound, a pharmaceutically acceptable salt thereof, or a solvated form thereof of Claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing (a) heteroatom(s), and the ring is a condensed ring with a benzene ring.

[Claim 4]

A compound, a pharmaceutically acceptable salt thereof, or a solvated form thereof of Claim 1, wherein the non-interfering substituent is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl.

(Omitted)

[Claim 23]

Formula (IX-2):

[Chemical formula 29]

(the description of the chemical formula is omitted)

(wherein Y is hydroxy; Z is an oxygen atom; C ring, Z1, Z^2, $Z^{3,}$ and R^1 have the same meaning as Claim 1; R^9, R^{10}, R^F, and R^G are each independently a non-interfering substituent of Claim 1, provided that when R^G is hydrogen and R^F is alkyl, C ring is not dihydropirimidine)."

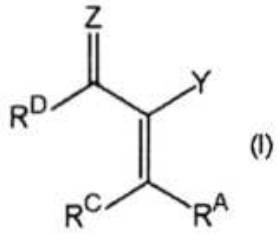
recited in the scope of claims before the amendment

is corrected to

"[Claim 1]

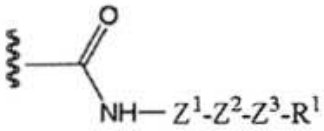
A pharmaceutical composition provided as an integrase inhibitor containing as an active ingredient a compound represented by the following formula (I):

[Chemical Formula 1]



(I)

(wherein
R^A is a group represented by the formula:
[Chemical Formula 3]



(wherein Z^1 and Z^3 are each independently 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 optionally substituted phenyl, optionally substituted 5- to 8-membered aromatic heterocyclic group, an optionally substituted cycloalkyl with a carbon number of 3 to 6 or optionally substituted heterocycle ('each substituent of optionally substituted' is, independently from the others, selected from an alkyl, haloalkyl, halogen, and alkoxy));

Y is hydroxy;

Z is an oxygen atom;

R^C and R^D taken together with the neighboring carbon atoms form a 5- to 6-membered ring containing (a) heteroatom(s), and the ring may be a condensed ring with a benzene ring;
the ring formed by R^C and R^D is optionally substituted with a group represented by the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above);

and the ring formed by R^C and R^D is optionally substituted, at any possible position other than that which is substituted with a group of the formula: -Z^1-Z^2-Z^3-R^1 (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above), with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, and alkenyl.),

a pharmaceutically acceptable salt or solvate thereof.

[Claim 2]

A pharmaceutical composition of Claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 5- or 6-membered ring containing an N atom.

[Claim 3]

A pharmaceutical composition of claim 1, wherein R^C and R^D taken together with the neighboring carbon atoms form a 6-membered ring containing (a) heteroatom(s)."

Then, the amendment can be said to be an amendment by which some of compounds represented by the formula (I) recited in Claim 1 before the amendment are left in claims 1 to 3. In addition, the amendment is not an amendment that allows a combination of specific alternatives, or specific compounds, to remain in the claims, nor is it an amendment that cannot be recognized as not introducing new technical matters unless the corresponding embodiment is stated in the description or the like originally attached to the application at the time of filling application for the Patent Invention. Therefore, it can be said that the amendment is within the matters stated in the description, scope of claims, or drawings originally attached to the application at the time of filling application for the Patent Invention.

Therefore, the patent for the Patent Invention cannot be invalidated by Reason for Invalidation 4.

5. Regarding Reason for Invalidation 5

In Claim 1, the recitation of " the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)" follows the recitation of "and the ring formed by R^C and R^D is."

Then, this recitation refers to "the ring formed by R^C and R^D." Thus, the recitation of "the formula: $-Z^1-Z^2-Z^3-R^1$ (wherein Z^1, Z^2, Z^3, and R^1 are the same as defined above)" is recognized to be also related to the recitation of " the ring formed by R^C and R^D"

Then, it is clear that "a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$" in this recitation cannot mean the group contained in [Chemical Formula 3] but means "a group represented by the formula: $-Z^1-Z^2-Z^3-R^1$," which may be substituted with a ring

formed by R^C and R^D.

Therefore, the recitation of Claim 1 is clear.

The recitation of Claims 2 and 3 are also clear.

Therefore, the patent for the Patent Invention cannot be invalidated by Reason for Invalidation 5.

No. 7.

As stated above, the patent for the Patent Inventions 1 to 3 should be invalidated due to Reasons of Invalidation 1 and 2.

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

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

August 8, 2017

Chief administrative judge: MURAKAMI, Kimitaka

Administrative judge: KURANO, Masaaki

Administrative judge: MAEDA, Kayoko