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D E C I S I O N
of 19 April 2005

Case Number: W 0019/04 - 3.3.2

Application Number: PCT/US03/12901

Publication Number: WO 03/090690 A2

IPC: A61K

Language of the proceedings: EN

Title of invention:
Cellular accumulation of Phosphonate Analogs of HIV Protease Inhibitor Compounds

Applicant:
Gilead Sciences, Inc.

Opponent:
-

Headword:
Phosphonate Analogs of HIV Protease Inhibitor Compounds/GILEAD SCIENCES

Relevant legal provisions:
EPC Art. 154(3)
PCT Art. 17(3)(a)
PCT R. 13.1, 40.1, 40.2

Keyword:
"Unity a priori (no) - no common structural element"
"Unity a posteriori (no) - common structural element anticipated"

Decisions cited:
W 0003/93

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0019/04 - 3.3.2

International Application No. PCT/US03/12901

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 19 April 2005

Applicant: Gilead Sciences, Inc.
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Foster City
CA 94404 (US)

Representative: Reitstötter-Kinzebach & Partner (GbR)
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D-81679 München (DE)

Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 10 November 2003.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
B. Günzel

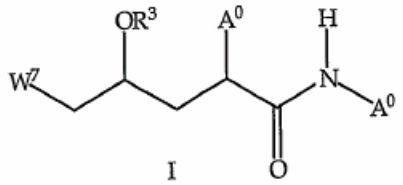
Summary of Facts and Submissions

I. The applicant filed an international patent application, No. PCT/US03/12901 (EP03747326.1), comprising a set of 200 claims, claims 1 to 3 of which read as follows:

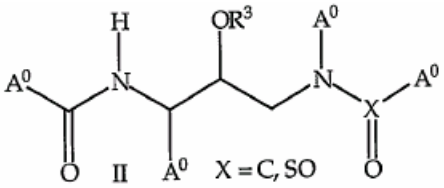
"1. An HIV protease inhibitor compound comprising a phosphonate group.

2. An HIV protease inhibitor compound of claim 1 selected from:
a Saquinavir-like phosphonate protease inhibitor compound,
a Lopinavir-like phosphonate protease inhibitor compound,
a Ritonavir-like phosphonate protease inhibitor compound,
a Indinavir-like phosphonate protease inhibitor compound,
a Atazanavir-like phosphonate protease inhibitor compound,
a Nelfinavir-like phosphonate protease inhibitor compound,
a Tipranavir-like phosphonate protease inhibitor compound,
a Amprenavir-like phosphonate protease inhibitor compound,
a KNI-like phosphonate protease inhibitor compound, and
a Cyclic Carbonyl-like phosphonate protease inhibitor compound;
and pharmaceutically acceptable salts, hydrates, and formulations thereof.

3. A compound selected from the Formulas:



I



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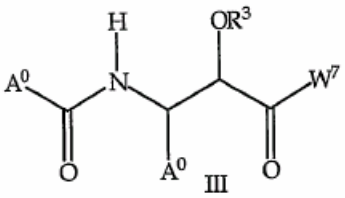

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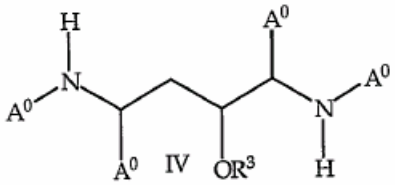

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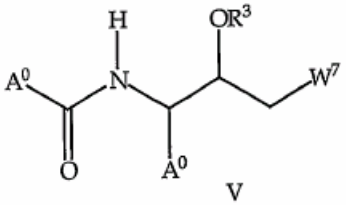

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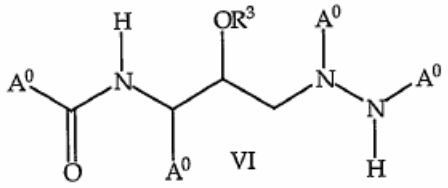

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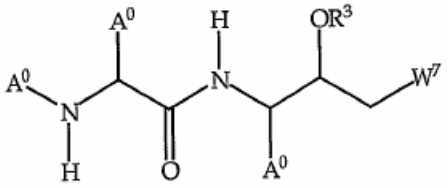
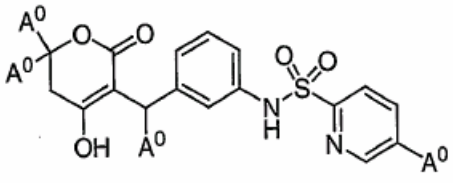


Va



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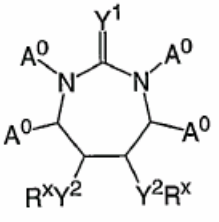
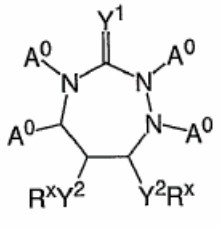
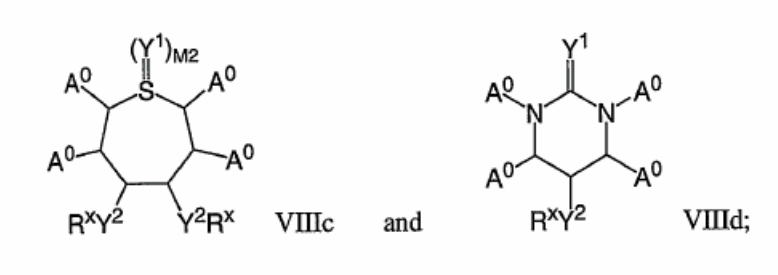


VIIIa



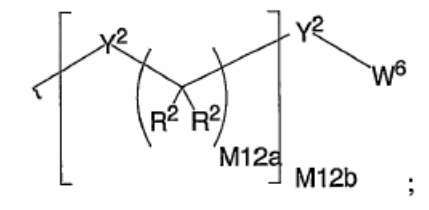
VIIIb



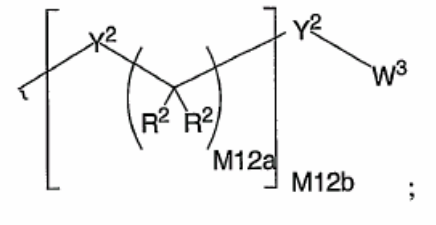
wherein:

A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

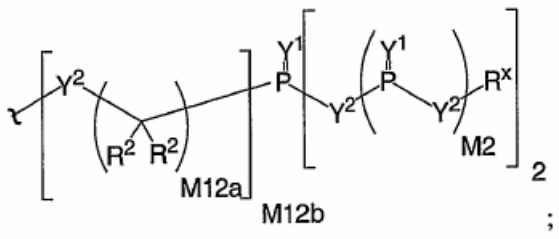
A^1 is:



A^2 is:



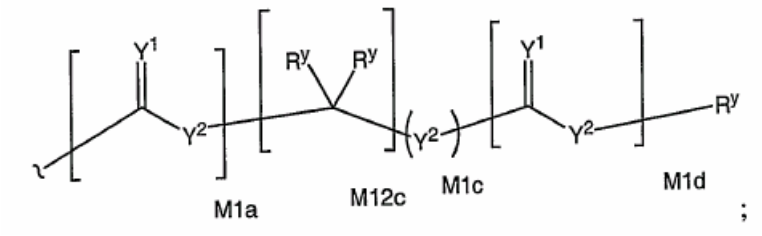
A^3 is:



Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^X)$, $N(O)(OR^X)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^X)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups, or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3C} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^l;

R^{3C} is $-R^x$, $-N(R^x)(R^x)$, $-SR^X$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^X)$, $-S(O)_2(OR^X)$, $-OC(Y^l)R^x$, $-OC(Y^l)OR^x$, $-OC(Y^l)(N(R^x)(R^x))$, $-SC(Y^l)R^x$, $-SC(Y^l)OR^X$, $-SC(Y^l)(N(R^x)(R^x))$, $-N(R^x)C(Y^l)R^x$, $-N(R^x)C(Y^l)OR^x$, or $-N(R^x)C(Y^l)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^l)R^x$, $-C(Y^l)OR^x$ or $-C(Y^l)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;
W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;
W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;
W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;
M2 is 0, l or 2;
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
M1a, M1c, and M1d are independently 0 or 1; and
Ml2c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or l2."

II. In its communication dated 10 November 2003, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to pay thirty-five additional search fees.

The ISA found that the present application consisted of several strains of inventions due to a priori and/or a posteriori non-unity.

The first strain of inventions (strain I) consisted of claims 1, 2, 130 to 137, 138, 139, 152, 153 and, partly, 190 to 192, 196 and 197 to 199, and was concerned with HIV protease inhibitor compounds which have to have a phosphonate group as the only common structural element.

The second strain of inventions (strain II; claims 3 to 92, 95 to 122, 140 to 151 and 154 to 165) was related to compounds of structures I to VIIId which did not

have to have a phosphonate group and therefore a priori did not exhibit unity with respect to the first strain.

Further strains of inventions were discussed, including arguments for a priori and a posteriori non-unity.

With respect to the first and second strains, WO-A-0004033 was cited because this document disclosed protease inhibiting compounds exhibiting phosphono-oxy groups. These compounds fell within the extremely broad definition of compounds containing phosphonate groups (claims 1 and 2 of the current application - the first strain) and of compounds containing a "protecting group" with respect to formula II of claim 3, substituent W^3 (the second strain).

Hence, the technical feature "comprising a phosphonate group" could no longer serve as a special technical feature, linking the different subjects of invention strain I together and the substituents of the structures I to VIIIb could no longer serve as special technical features linking the different structures of invention strain II together.

Accordingly, *inter alia* the following groups of inventions were identified by the ISA:

"1. Claims: partly: 1, 2, 130—136
Saquinavir-like HIV protease inhibitor compounds and their use
2. Claims: partly: 1, 2, 130—136
Lopinavir-like HIV protease inhibitor compounds and their use

3. Claims: partly: 1, 2, 130—136
Ritonavir-like HIV protease inhibitor compounds and their use
4. Claims: partly: 1, 2, 130—136
Indinavir-like HIV protease inhibitor compounds and their use
5. Claims: partly: 1, 2, 130—136
Atazanavir-like HIV protease inhibitor compounds and their use
6. Claims: partly: 1, 2, 130—136
Nelvinavir-like HIV protease inhibitor compounds and their use
7. Claims: partly: 1, 2, 130—136
Tipranavir-like HIV protease inhibitor compounds and their use
8. Claims: partly: 1, 2, 130—136
Amprenavir-like HIV protease inhibitor compounds and their use
9. Claims: partly: 1, 2, 130—136
KNI-like HIV protease inhibitor compounds and their use
10. Claims: partly: 1, 2, 130—136
Cyclic carbonyl-like HIV protease inhibitor compounds and their use
11. Claims: partly: 1, 130—136
HIV protease inhibitor compounds comprising a phosphonate group which are not comprised by inventions 1 to 10 and their use
12. Claims: 4, partly: claims 3, 15—88, 95, 96
compounds of formula I according to claim 3
13. Claims: 5, 89—91, 97—113, partly: claims 3, 5, 15—88, 95, 96
compounds of formula II according to claim 3
14. Claims: 6, partly: claims 3, 15—88, 95, 96
compounds of formula III according to claim 3

15. Claims: 7, partly: claims 3, 15—88, 95, 96
compounds of formula IV according to claim 3
16. Claims: partly: claims 3, 8, 15—88, 95, 96
compounds of formula V according to claim 3
17. Claims: partly: claims 3, 8, 15—88, 95, 96
compounds of formula Va according to claim 3
18. Claims: 9, partly: claims 3, 15—88, 95, 96
compounds of formula VI according to claim 3
19. Claims: 10, partly: claims 3, 15—88, 95, 96
compounds of formula VII according to claim 3
20. Claims: 11, 114, 115, 118—122, partly: claims 3, 15—88, 95, 96
compounds of formula VIIIa according to claim 3
21. Claims: 12, partly: claims 3, 15—88, 95, 96
compounds of formula VIIIb according to claim 3
22. Claims: 13, partly: claims 3, 15—88, 95, 96
compounds of formula VIIIc according to claim 3
23. Claims: 14, partly: claims 3, 15—88, 95, 96
compounds of formula VIIId according to claim 3"

III. With its reply, dated 23 December 2003, the applicant paid twenty-one additional search fees under protest pursuant to Rule 40.2(c) PCT and requested that additional searches be carried out with regard to inventions 2 to 10 and 12 to 23 as outlined in the invitation to pay additional fees.

In support of the protest, the applicant argued that unity was given for:

"Inventions 1 and 17;
Inventions 2, 3 and 15;
Inventions 4 and 12;
Inventions 5 and 18;

Inventions 6 and 16;
Inventions 7 and 19;
Inventions 8 and 13;
Inventions 9 and 14; and
Inventions 10 and 22 to 23".

The compounds of claim 3 were defined by formulae I to VIIId and had a phosphonate group in the same way as the compounds of claims 1 and 2. It should be noted that each formula carried several radicals A^0. By definition of A^0, each compound of claim 3 necessarily contained at least one A^3 group. The formula of A^3 was given in claim 3 and included a phosphonate group. This phosphonate group contained the phosphorus atom, an organic residue bonded to the phosphorus atom ("from the left side") and substituents Y^1 and Y^2.

As a consequence, the first and second strains of the inventions did not lack a priori unity since they had a common structural element which was the phosphonate group.

Additionally, the applicant showed structural similarities between individual inventions in the list cited above, in so far as they were written in one line.

It requested that the search fees be refunded if unity was determined in its favour, in particular for inventions 12 to 23.

IV. In a prior review pursuant to Rule 40.2(e) PCT, dated 20 April 2004, the review panel of the ISA found the

invitation to pay additional fees to be justified and invited the applicant to pay the protest fee.

In summary, the review panel considered that the applicant had paid twenty-one additional search fees and had requested that searches be carried out for inventions 2 to 10 and 12 to 23. As the applicant was of the opinion that some of these inventions for which search fees had been paid were unitary (see the applicant's list of nine separate "unified" inventions on page 2 of its protest letter and as cited above), it wished only to pay for eight additional searches and consequently requested the refund of thirteen search fees.

In its invitation to pay additional fees, the ISA found both non-unity a posteriori and a priori. The presence of a posteriori non-unity had not been questioned by the applicant. Only the presence of a priori non-unity was denied.

The review panel agreed with the applicant's argument that the substituent definitions in claim 3 of the application for Y^1 and Y^2 were responsible for the nature of the claimed compounds. However, since Y^2 could be a bond instead of a substituent, the phosphonic acid phosphides or phosphinous acid derivatives contained in the resulting compounds were clearly not phosphonates und thus exhibited no common structural element with the compounds of claim 2.

Therefore, referring to the statement of non-unity of the subject-matter of claims 2 and 3, the review panel

was of the opinion that the ISA was right in its conclusions.

V. With a letter of 21 May 2004, the applicant paid the protest fee according to Rule 40.2(e) PCT.

Reasons for the Decision

1. Under Article 154(3) EPC, the boards of appeal are responsible for deciding on the protest made by the applicant.

2. The protest complies with the requirements of Rule 40.2(c) PCT and is therefore admissible.

3. The relevant aspects of the general requirements for protest proceedings pursuant to Rule 40.2 PCT are as follows:

3.1 Pursuant to Rule 40.2 PCT, the board must examine the protest and, to the extent that it finds the protest justified, order the full or partial reimbursement to the applicant of additional fees, in so far as they were in fact paid and the payment was made under protest.

3.2 According to the established practice of the boards of appeal, the examination in protest proceedings has to be carried out in the light of the reasons given by the ISA in its invitation to pay additional fees under Rule 40.2 PCT and the applicant's submissions in support of the protest. The board cannot investigate of its own motion whether an objection relating to

non-unity of invention might be justified for other reasons not considered in the ISA's invitation to pay additional fees (see W 3/93, OJ EPO 1994, 931).

4. In the present case, the applicant paid twenty-one additional search fees for the ISA to carry out searches for inventions 2 to 10 and 12 to 23. However, it requested that the unity of 10 pairs or triples of invention groups belonging to invention strains I and II be acknowledged and that search fees be refunded in so far as unity was determined.

With respect to this request and to the ISA's invitation to pay additional search fees, a decision has to be taken on the basis of whether or not invention strains I and II a priori exhibit a single general inventive concept.

Consequently, any statements by the ISA in the invitation to pay additional search fees other than on a priori non-unity are not to be considered in this case.

4.1 With respect to invention strains I and II, the ISA's invitation to pay additional fees was based on the finding that all the different compounds being the subject-matter of claims 1 to 3 were intended to contain a phosphonate group as a single general inventive concept.

This conclusion was not contested by the applicant in its statement under Rule 40.2(c) PCT.

The board sees no reason to differ.

Additionally, the board agrees with the applicant's submission (see letter dated 23 December 2003, page 2, paragraphs 5 and 6) that the question of the presence or absence of a phosphonate group in the compounds of claim 3 has to be decided by considering the meaning of Y^1 and Y^2 with reference to the formula representing the substituent A^3 (see claim 3 as originally filed, page 1649, line 11).

4.2 According to the application in suit (see page 9, lines 21 to 27), the terms "phosphonate" and "phosphonate group" mean "a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, and nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, phosphondiamidate and phosphonthioate functional groups".

With regard to this definition, a group comprising a phosphorus-carbon bond, a phosphorus-oxygen double bond (Y^1 = O) and, for instance, a phosphorus-phosphorus bond (Y^2 = "a bond") is not a "phosphonate group" (see claim 3 of the application as filed, page 1649, lines 12 to 14). Alternatively Y^1 being bound to P as $P=Y^1$ could be S or monosubstituted N or N(O). The resulting groups in these cases are not "phosphonate groups" according to the given definition either.

Thus, the ISA's statement that compounds being the subject-matter of claims 1 and 2 (invention strain I) exhibit a phosphonate group obligatorily and that some compounds being the subject-matter of claim 3 (invention strain II) do not exhibit a phosphonate group is found to be true.

Consequently the special technical feature "presence of a phosphonate group" is not a common feature of these strains and cannot link them in the sense of a single general inventive concept.

4.3 These conclusions remain valid despite the applicant's attempts to show, together with the statement about the common "phosphonate group", similarities between representatives of the compounds claimed in claims 2 and 3, respectively.

On the one hand, the common "phosphonate group" is in fact missing and, on the other, the similarities seem accidental with respect to the complex structures of the known protease inhibitor compounds of claim 2.

Therefore, the alleged unity of invention groups according to the applicant's letter dated 23 December 2003 cannot be acknowledged.

5. As regards the additional search fees paid for searching invention groups 2 to 10 and 12 to 23, for the reasons given in point 4 of this decision, the board finds the applicant's protest not to be justified, so that the protest has to be dismissed.

Since the protest is not successful, there can be no refund of the fee for the examination of the protest.

Order

For these reasons it is decided that:

The protest is dismissed.

The Registrar: The Chairman:

C. Eickhoff U. Oswald