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D E C I S I O N
of 16 July 1996

Case Number: W 0006/95 - 3.3.1

Application Number: PCT/US 94/10536

Publication Number: -

IPC: -

Language of the proceedings: EN

Title of invention:
Pyrimidine derivatives for labeled binding partners

Applicant:
Gilead Sciences, Inc.

Opponent:
-

Headword:
Pyrimidine derivatives/GILEAD

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13, 40
Administrative Instructions under the PCT, Annex B, Part 1(f)

Keyword:
"Common new property (yes)"
"Significant structural element (yes)"

Decisions cited:
G 0001/89

Catchword:
-

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Case Number: W 0006/95 - 3.3.1
International Application No. PCT/US94/10536

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 16 July 1996

Applicant: Gilead Sciences, Inc.
353 Lakeside Drive
Foster City, California 94404 (US)

Representative: -

Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation of the European Patent Office (International Searching Authority) to pay additional fees dated 6 February 1995.**

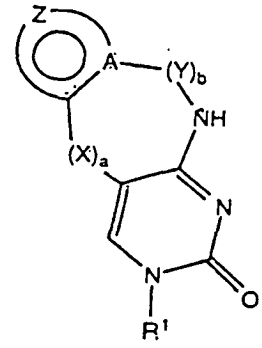
Composition of the Board:

Chairman: A. Nuss
Members: R. Spangenberg
R. Teschemacher

Summary of Facts and Submissions

I. Following the filing of International Patent Application No. PCT/US94/10536 the EPO, acting as ISA, on 6 February 1995 issued an invitation to pay within 45 days four additional search fees (Article 17(3)(a) and Rule 40.1 PCT).

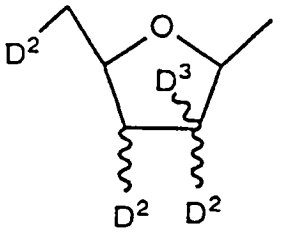
II. The said International Patent Application contained 30 claims, Claim 1 concerning compounds having the structure



(1)

wherein R^1 is a binding partner, a linker or H;
a and b independently are 0 or 1, provided that the total of a and b is 0 or 1;
A is independently N or C;
X is independently S, O, -C(O)-, NH or NCH_2R^6;
Y is -C(O)-;
Z is taken together with A to form an aryl or heteroaryl ring structure comprising 5 or 6 ring atoms wherein the heteroaryl ring comprises a single O ring heteroatom, a single N ring heteroatom, a single S ring heteroatom, a single O and a single N ring heteroatom separated by a carbon atom, a single S and a single N ring heteroatom separated by a carbon atom, 2 N ring heteroatoms separated by a carbon atom, or 3 N ring heteroatoms at

least two of which are separated by a carbon atom, and wherein the aryl or heteroaryl ring carbon atoms are unsubstituted with other than H or at least 1 nonbridging ring carbon atom is substituted with R^6 or =O;
R6 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, NO_2, $N(R^3)_2$, CN or halo, or an R^6 is taken together with an adjacent R^6 to complete a ring containing 5 or 6 ring atoms;
R^3 is a protecting group or H; and tautomers, solvates and salts thereof;
and provided that where a is 0, b is 1, and R^1 is



in which D^2 is independently hydroxyl, blocked hydroxyl, mono, di or triphosphate, or an oligodeoxyribonucleotide otherwise containing only the bases A, G ,T and C; and D^3 is H or OH;
then Z is not unsubstituted phenyl.

Claims 2 to 16 related to certain sub-groups of compounds of the above formula;
Claims 17 to 21 to chemical compounds useful for preparing the compounds of formula (1) ("intermediates");
Claims 22 to 27 and 29 to oligonucleotides containing at least one base of the structure indicated in Claim 1, bound to the oligonucleotide at the N-atom carrying the substituent R^1 in formula (1);

Claim 28 to a method making use of the compound of Claim 22; and
Claim 30 to a method making use of a broad class of compounds, including those of Claim 22.

The ISA cited document

D1: JP-A-62/059293 (Chem. Abstr. 107 : 7526n)

and held that it disclosed compounds which fell within the scope of the proviso of claim 1, namely 2-(2-deoxy-beta-A-erythro-pentofuranosyl)-pyrimido-(4,5-c)isoquinoline-3,6-(2H,4H)-dione and its mono- di- and tri-phosphate derivatives, which were useful as components of oligo- or poly-nucleosides and could serve as fluorescent probes. In respect of that state of the art, the ISA identified the technical problem underlying the international patent application to be the provision of further compounds serving the same purpose. Three different solutions of this problem were found to be contained in the above Claim 1, namely

1. the compounds of formula (1), where a=0 and b=0 ;
2. the compounds of formula (1) where a=0 and b=1;
3. the compounds of formula (1), where a=1 and b=0;

these sub-classes of compounds having no novel structural or functional technical feature in common and represented therefore three different inventions not so linked as to form a single general inventive concept (hereinafter "invention 1", "invention 2" and "invention 3") (Rules 13.1 to 13.3 EPC).

The ISA further held that the intermediate compounds of Claim 21 (hereinafter "invention 4") could not be fairly said to belong to any one of the above-identified inventions, since they were structurally too different

from the compounds of formula (1), and that the method of Claim 30 in so far as it did not make use of an oligonucleotide of claim 22 (hereinafter "invention 5"), did also form a separate invention.

III. On 20 March 1995 the Applicant paid four additional search fees and indicated that three of them were paid under protest (Rule 40.2(c) PCT). He did not protest against the invitation to pay an additional search fee for "invention 5". In respect of the other four "inventions" he submitted that "a priori" these inventions shared a common inventive concept, and that the ISA had found lack of unity of invention only "a posteriori" on the basis of an objection of lack of inventive step. In his opinion, the ISA had not substantiated its finding, since it only alleged that the compounds covered by Claim 1 had properties identical with those excluded from that claim by the proviso contained in it, but failed to take into account that D1 was solely concerned with the problem of introducing base-pairing fluorescent pyrimidine nucleoside analogues into oligonudeotides in order to improve the detection of the oligonudeotides by fluorescence means, and was silent about the affinity of such compounds, so that it expressed no concern or interest about the problem underlying the present application.

In respect of "invention 4" he submitted that Claim 21 related to intermediates used in the preparation of the compounds of "invention 2", which had no disclosed utility other than in the preparation of the compounds of "invention 2" and should therefore be considered to represent embodiments of the same inventive concept.

He therefore requested that three additional search fees be refunded.

IV. On 11 July 1995 the result of the prior review provided for in Rule 40.2(e) PCT was communicated to the Applicant, who was also invited to pay the protest fee. The Review Panel found the protest justified in respect of the intermediate compounds of "invention 4", but maintained the view expressed in the invitation in respect of the other two of the three search fees paid under protest. It considered Part 1 (f)(i) of Annex B of the Administrative Instructions under the PCT. The Rewiew Panel stated that the technical problem defined by the Applicant was already known and solved. The Review Panel held that at most the compounds of "invention 3" solved the problem of increasing the hybrid stability over the known level, whereas the compounds according to "invention 1" and "invention 2" were merely alternatives having the same effect as a compound of the state of the art. The common technical problem solved by all three "inventions" was thus seen in providing further pyrimidine nucleotide analogues suitable for enhancing hybrid stability in respect of the natural pyrimidine. This problem was said to be a well known desideratum which was achieved by quite different inventive concepts, since the three groups of compounds did not share a common novel structural feature.

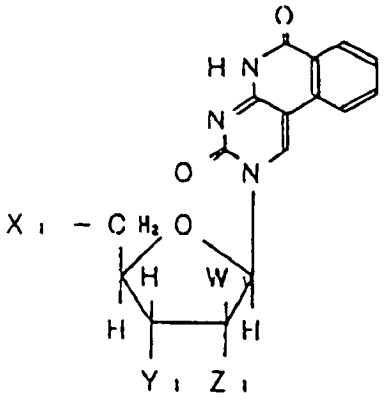
On 9 July 1993 the Applicant paid the protest fee.

Reasons for the Decision

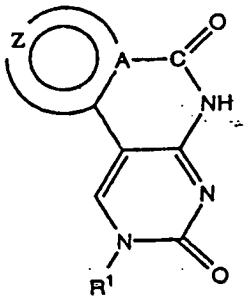
1. The protest is admissible.

2. The only question that remains to be decided (see point III above) in respect of the present protest is whether "invention 1" to "invention 3" (see point I above) belong to one single inventive concept, as required by Rule 13.1 and defined in Rule 13.2 PCT.

3. The objection of non-unity was raised by the ISA **a posteriori**, i.e. taking into account the state of the art formed by D1, which relates, inter alia, to compounds of the following formula:



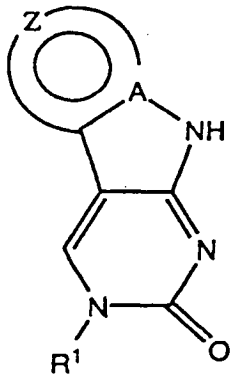
belonging to the compounds of formula (1) (see point II above, wherein a is 0 and b is 1 (see the following formula (1-2))



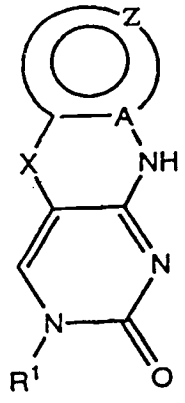
formula (1-2)

which are excluded from Claim 1 by way of disclaimer (see point II above, the proviso at the end of Claim 1, which should correctly refer to "Z together with A" instead of "Z", as had been rightly observed by the ISA). The proviso in Claim 1 requires that, if R^1 means a sugar residue of the type present in the compounds of D1 and Z together with A means a phenyl ring, then this phenyl ring must carry at least one substituent.

For "invention 1" (wherein a is 0 and b is 0, see formula (1-1) below) and "invention 3" (wherein a is 1 and b is 0, see formula (1-3) below)



formula (1-1)



formula (1-3)

the proviso is not applicable, so that in these compounds a phenyl ring formed by A and Z may be unsubstituted.

4. It follows from Part 1 (f)(i) of Annex B of the Administrative Instructions under the PCT, which are binding not only for the ISA but also for the Board of Appeal acting as the "three-member board" according to Rule 40.2(c) PCT (see decision G 1/89 of the Enlarged Board of Appeal, OJ EPO 1991, 155) that it is not sufficient, in order to establish unity of invention "a posteriori" that all alternatives of chemical compounds covered by a Markush claim have a common property or activity, i.e. are suitable for solving a common

technical problem, because according to item (B)(1) they must, in addition, have a "significant structural element" in common in order for the alternatives to form unity.

5. In the Board's judgment, it is, however, not in agreement with the explanation given in Part 1 (f)(ii) of Annex B of the Administrative Guidelines under the PCT to assume that the said "significant structural element" must be novel **per se**. Rather, this expression means that **in relation to the said common property or activity** there must be a common part of the chemical structure which distinguishes the claimed compounds from known compounds having the same property or activity.

6. Neither in the invitation nor in the reasoned statement of the review panel it is, however, disputed that all the claimed compounds have **two properties** in common, namely

- the property of enhancing the binding affinity of oligonucleotides containing them for oligonucleotides having complementary sequences in respect of a control oligonucleotide 5-methyl deoxy-C (i.e. the natural pyrimidine identified by the review panel) instead of the claimed cytidine derivatives (see description of the present patent application, pages 31 to 33), and

- the property of bearing a readily detectable characteristic (see the description of the present patent application, page 1, lines 6 to 9).

It is also not in dispute that the known compounds having the first property are structurally different from the claimed ones in that they do not contain the "polycyclic substructure" (i.e. the part of the claimed compounds except the substituent R^1), whereas D1, which describes compounds having such a substructure, relates only to the second property.

7. The international search has thus not revealed any chemical compound which was known to have both properties.

Therefore, starting either from the state of the art acknowledged in the description of the present patent application and referred to by the review panel (obviously WO 92/10115 relating to 5-substituted pyrimidine bases such as 5-propinyl-dC) which enhance the binding affinity for complementary sequences, or, as did the ISA, from D1 relating to oligonucleotides having a readily detectable characteristic, the technical problem underlying the present patent application can be seen to be the provision of oligonucleotides (and intermediates for their preparation) that are modified to enhance their binding affinity for complementary sequences and that **in addition** bear a readily detectable characteristic, as stated in the first paragraph of the description of the present patent application.

8. As already stated (see point 6 above) it is not in dispute that this technical problem was solved by the claimed compounds.

However, neither the invitation nor the reasoned statement of the review panel sets out a logical line which would have led a person skilled in the art to that solution of the said technical problem, and which would destroy the single general inventive concept within the meaning of Rule 13.1 PCT.

9. Therefore, there is at least no **clear** reason why the present claim 1 should relate to obvious subject-matter (see G 1/89, point 8.2 of the reasons, which explains that an objection of non-unity should only be raised a posteriori in clear cases). In the present case, the fact that chemical compounds are known which fall within the proviso contained in Claim 1 of the present patent application is thus not sufficient to destroy the unity of the claimed invention, since these known compounds were not known to have the property of enhancing the binding affinity of oligonucleotides containing them for oligonucleotides having complementary sequences, in respect of a control oligonucleotide containing 5-methyl deoxy-C. The common structural feature conferring this property to the claimed compounds is to be seen, in the Board's judgment, in the above-mentioned "polycyclic substructure". The requirements for unity of invention in respect of a "Markush-claim" set out in Part 1(f) of Annex B of the Administrative Instructions under the PCT are thus met in the present case.

10. For the reasons set out above the two additional search fees and the protest fee cannot be retained (Rule 40.2(c) and (e) PCT).

Order

For these reasons it is decided that:

1. The protest is allowed.

2. The refund of two search fees and the protest fee is ordered.

The Registrar: The Chairman:

E. Görgmaier A. Nuss