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D E C I S I O N
of 11 December 2003

Case Number: T 0104/00 - 3.3.1

Application Number: 91902085.9

Publication Number: 0506830

IPC: C07D 413/12

Language of the proceedings: EN

Title of invention:
Uncharged morpholino-based polymers having phosphorous-containing chiral intersubunit linkages

Applicant:
ANTIVIRALS INC.

Opponent:
-

Headword:
Morpholino-based oligonucleotides/ANTIVIRALS

Relevant legal provisions:
EPC Art. 123(2), 84, 56

Keyword:
"Amendments - supported by the application as filed (yes)"
"Clarity (yes) - functional definition of limited class of chemical substituents partly structurally defined"
"Novelty (yes)"
"Inventive step (yes) - non-obvious solution"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0104/00 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 11 December 2003

Appellant: ANTIVIRALS INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 27 July 1999 refusing European application No. 91902085.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. F. Ranguis
S. C. Perryman

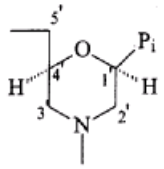
Summary of Facts and Submissions

I. This appeal lies against the decision of the Examining Division refusing European patent application No. 91 902 085.9 (Publication number No. 0 506 830) pursuant to Article 97(1) EPC.

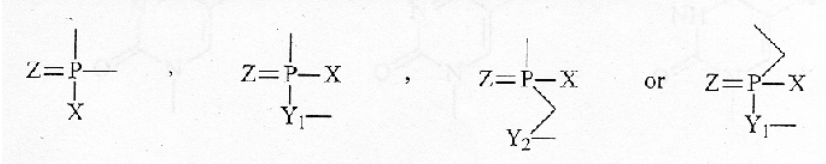
II. The decision under appeal was based on three requests submitted at the oral proceedings before the Examining Division.

Claim 1 of the main request read as follows:

"A polymer composition comprised of morpholino subunit structures of the form:

(A) 

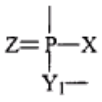
where (i) the structures are linked together by uncharged, chiral linkages, one to three atoms long, joining the morpholino nitrogen of one subunit to the 5' exocyclic carbon of an adjacent subunit, and (ii) P_i is a purine or pyrimidine base-pairing moiety effective to bind by base-specific hydrogen bonding to a base in a polynucleotide, and wherein the linkage (i) is selected from



wherein X is F; CH_2R; OCH_2R; -S-CH_2R; NR_1R_2 where R is H, CH_3 or other moieties that do not interfere with target binding and R_1 and R_2 may be the same or different and

selected from R or cyclic aliphatic or aromatic moiety; Y_1 is O, S, CH_2 or NR; Y_2 is O, S or CH_2; and Z is O or S".

Claim 1 of the first auxiliary request differed from Claim 1 of the main request essentially in that linkage (i) was selected from



The second auxiliary request was considered allowable by the Examining Division subject to amendment of the description. It was however subsequently withdrawn by the Applicant in order to allow him the opportunity of an appeal.

III. In its decision, the Examining Division considered that starting from document

(1) WO-A 86/05518

as the closest state of the art, the technical problem to be solved could be viewed in the provision of further polymers which were capable of sequence specific binding to polynucleotides. Since document (1) disclosed polymers comprised of morpholino subunits joined by uncharged, predominantly (i.e. not exclusively) achiral linkages, chiral linkages such as phosphorous-containing linkages were not excluded. Since phosphorous containing linkers had already been considered in nucleosides in document

(2) Nucleic Acid Res. 17 (1989), pp. 6129-6141,

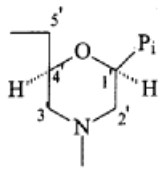
the claimed solution to the technical problem was obvious in view of the teaching of documents (1) and (2).

Nor could an inventive step be acknowledged if the technical problem to be solved was viewed in the provision of new compounds having improved RNA-binding properties. Such an improved result could not be recognized within the whole claimed area.

It was, furthermore, considered that the expression "or other moieties that do not interfere with the target binding" gave rise to an objection under Article 84 EPC.

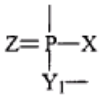
IV. Oral proceedings took place before the Board on 11 December 2003. The Appellant filed at these oral proceedings as sole request a set of nineteen claims, independent Claims 1 and 14 reading as follows:

"1. A polymer capable of sequence specific binding to a single stranded polynucleotide, comprised of morpholino subunit structures of the form:

(A) 

wherein (i) the structures are linked together by uncharged, chiral linkages, joining the morpholino nitrogen of one subunit to the 5' exocyclic carbon of an adjacent subunit, and (ii) P_i is a purine or pyrimidine base-pairing moiety effective to bind by base-specific hydrogen bonding to a base in a

polynucleotide, and wherein the linkage (i) is selected from



wherein X is F; CH_2R; OCH_2R; -S-CH_2R or NR_1R_2 where each of R, R_1 and R_2 are H, CH_3 or another moiety that does not interfere with target binding; Y_1 is joined to the 5' exocyclic carbon of the morpholino subunit; Y_1 is O, S, CH_2 or NR; and Z is O or S".

"14. A method for detecting, in a sample, the presence of a polynucleotide having a selected target sequence, comprising:
- contacting a polymer of any one of claims 1 to 13 with said polynucleotide, where said polymer (i) has a series of base-pairing moieties capable of binding to the selected target sequence, and (ii) is labelled with a detectable reporter group, where said reacting of the polymer with the polynucleotide is carried out under conditions effective to allow formation of a hybridization complex between the polymer and the target sequence; and
- detecting the presence of the reporter group".

V. The Appellant's arguments submitted at the oral proceedings and in the written proceedings as far as they are relevant for the present request, may be summarised as follows:

The present invention related to polymers having morpholino structures of the formula (A) as nucleoside analogues, which were linked together by chiral linkages of the formula -P(=Z)(X)-Y_1-, and hence resulting in atactic polymers, capable of sequence

binding to a single stranded polynucleotide. Contrary to the opinion of the Examining Division, document (1) warned against the use of chiral linkages moieties on the ground that the atactic resulting polymers would be impractical to purify and could generate toxic side effects in therapeutic applications or give misleading diagnostic values. The teaching of document (2) was wholly in accordance with that of document (1). Furthermore document

(3) Froehler et al, Nucleic Acids Research, 1988, **16**, pp 4831-4839

confirmed that polymers having deoxyribonucleoside subunits linked by phosphoramidate linkage moieties, i.e., that type of linkage moieties envisaged in the claimed invention, bound more weakly to a target than the complementary DNA strand.

There was, therefore, nothing in the prior art to suggest that morpholino subunits and phosphorus containing chiral linkages could be combined to achieve effective binding to a polynucleotide target.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of Claims 1 to 19 submitted at the oral proceedings on 11 December 2003.

VII. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Amendments - Article 123(2) EPC

2.1 The first part of Claim 1 relating to the functional and structural definition of the polymer is supported by the application as originally filed on page 4, line 25 to page 5, line 8; page 7, lines 21 to 22 and Figure 3B. The second part of Claim 1 relating to the meanings of the substituents X, Y_1, and Z finds support in the application as originally filed on page 5, lines 25 to 30 and in Figure 3B for the citation that Y is bound to the 5´ exocyclic carbon of the morpholino subunit. In particular, regrouping the meanings of R, R_1 and R_2 as here in the present Claim 1, whereas R, on the one hand, and R_1, R_2, on the other hand, were separately defined in the application as filed (cf. page 5, lines 26 to 29) does not extend the content of the application as filed since this amounts to deletion of the cyclic aliphatic or aromatic moieties from the meanings of R_1 and R_2, i.e. a restriction operated within a single list of substituents.

2.2 The subject-matter of Claims 2 to 5 corresponds respectively to that of Claims 2, 4, 6 and 7 as originally filed. The subject-matter of Claim 6 amounts to a restriction of the meaning of Y_1 as originally filed operated within a single list of substituents (cf. page 5, line 29). The subject-matter of Claims 7 to 12 corresponds respectively to that of Claims 10 to 15 as originally filed. Support for the subject-matter of Claims 13 and 19 can be found on page 27, lines 9 to 10

of the application as originally filed. The subject-matter of Claim 14 finds support on page 26, lines 16 to 25 of the application as originally filed. The subject-matter of Claims 15 to 18 is supported by the application as filed respectively on page 26, lines 21 to 22; page 26, line 18 (DNA), page 26, line 18 (RNA) and page 31, lines 3 to 4.

2.3 There is thus no objection under Article 123(2) EPC.

3. *Article 84 EPC*

3.1 The sole question, in the Board's judgment, is whether or not in Claim 1 the feature "X is CH_2R; OCH_2R; $-S-CH_2R$ or NR_1R_2 **where each of R, R_1 and R_2 are H, CH_3 or another moiety that does not interfere with target binding**" gives rise to an objection under Article 84 EPC for lack of clarity.

3.2 The Appellant provided a declaration executed by Dr Dwight Weller, an inventor of the present application, explaining that the determination of suitable substituents for the groups $-CH_2-$, $-OCH_2-$, $-SCH_2-$ or -N< for a given polymer, i.e. a "moiety that does not interfere with target binding", could be achieved by assessing the ability of a nucleic acid analogue to bind to a target sequence by determining the melting temperature (Tm), a standard laboratory technique, of a duplex formed by the nucleic acid analogue and the target sequence.

3.3 The Board concurs with the Appellant that measuring the melting temperature (TM) of a duplex only requires well-known routine testing. The feature "another moiety

that does not interfere with target binding" is, therefore, accepted as a functional feature directed to a desirable result to be achieved.

However, if structurally undefined chemical substituents are part of the invention to be protected, they cannot be merely defined in the claim in terms of a desirable result to be achieved if that kind of functional feature is not indicative of the substituents within the scope of the claim. In the absence of common general knowledge in this respect, as is the case here, the claim must lay out relevant indications pointing to the suitable structures of the substituents in order not to leave the skilled person at a loss regarding the substituents covered by the claim. It goes without saying that the sufficiency of such indications must be assessed on a case by case basis.

3.4 In the present case, Claim 1 does not merely contain a functional definition for characterizing undefined structural elements by using a standard laboratory test but also contains relevant indications regarding the basic structure of the feature "X" ("CH_2R; OCH_2R; -S-CH_2R; NR_1R_2 where each of R, R_1, R_2 may be H, CH_3, in addition to a moiety that does not interfere with the target binding").

Although not exhaustive in respect of the moieties not interfering with target binding, this limiting definition of feature "X" (cf. point 2.1 above) is in this case, in the Board's judgment, a sufficiently precise definition of the substituents R, R_1, R_2. Indeed, with the help of the above mentioned routine test, by

making comparison to the binding values for the cases where the substituents are H or CH_3, suitably binding structures with analogue substituents R, R_1 and R_2 can be determined. The whole expression "X is CH_2R; OCH_2R; -S-CH_2R; NR_1R_2 where each of R, R_1 and R_2 are H, CH_3 or other moieties that do not interfere with target binding" is, therefore, clear so that Claim 1 meets the requirements of Article 84 EPC.

4. *Article 54 EPC - Novelty*

After examination of the cited prior art documents, the Board has reached the conclusion that the subject-matter as defined in the claims of the present request is novel. Since novelty was never contested by the Examining division, it is not necessary to give detailed reasons for this finding.

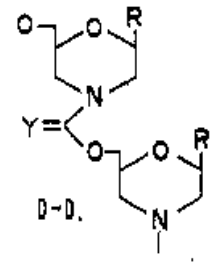
5. *Article 56 EPC - Inventive step*

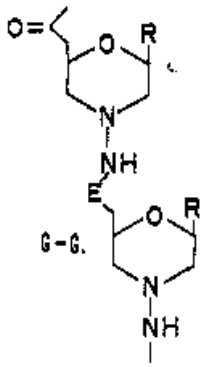
5.1 The claimed invention as reflected by Claim 1 of the present request relates to a polymer capable of sequence specific binding to a single stranded polynucleotide, comprised of morpholino subunit structures.

5.2 In a first step, the closest state of the art is to be determined.

5.2.1 Document (1) discloses polymers designed to bind, with a selected binding affinity, to a polynucleotide containing a target sequence of bases, comprised of backbone moieties supporting recognition moieties and joined by chemically stable, substantially uncharged,

predominantly achiral linkages (cf. page 7, line 20 to page 8, line 16). In particular, are disclosed polymers comprised of morpholino subunits joined by carbamate, thiocarbamate, hydrazide or sulfonyl hydrazide linkages as set out in Figure 6, formulae D-D and G-G below





wherein Y is O, S and E is C=O or O-S=O (cf. Claim 4), R are recognition moieties selected from purine or pyrimidine (cf. Claim 1).

5.2.2 Document (2) discloses an oligonucleotide analogue comprised of morpholino subunits linked by carbamate linkages (cf. page 6134). This disclosure overlaps, therefore, that of document (1), while being limited to a single oligonucleotide.

5.2.3 Both documents aim at the same objective as the claimed invention. The named inventors of Document (1) are the authors of document (2) issued four years later. Since document (1) can be seen as the parent disclosure from which document (2) derives and since the disclosure of document (1) is more exhaustive than that of document

(2), document (1) is, in the Board's judgment, the more appropriate starting point for defining the technical problem to be solved.

5.3 In the light of this closest state of the art, the technical problem underlying the patent in suit may be seen, as already formulated by the Examining Division and submitted by the Appellant, in the provision of further polynucleotide analogues capable of sequence binding to single stranded polynucleotides.

The Board has no reason to doubt that the technical problem is solved within the entire claimed area.

5.4 The Appellant contested the decision of the Opposition Division according to which it could be derived from document (1) that chiral linkages, in particular phosphorous-containing linkages, were not excluded due to the fact that the expression "predominantly achiral" did not bar the use of chiral groups.

5.5 The expression "predominantly achiral" in that document must be understood in the context of the material teaching actually provided by the disclosure as a whole.

The chemical structures of the cyclic backbone moieties actually disclosed are set out in Figure 6 (cf. A-A to G-G). The cyclic backbone moieties are joined by carbamate or thiocarbamate bonds (cf. Figure 6, A-A to D-D and page 32, line 32 to page 33, line 4) or ester, hydrazide or sulfonylhydrazide (cf. Figure 6, F-F and G-G and page 36, lines 28 to 32). All the subunit linkages are achiral (cf. page 33, lines 4 to 5 and page 37, lines 3 to 4). The technical teaching of this

disclosure relates, therefore, to oligonucleotides the backbone moieties of which are joined by achiral linkages. This is also confirmed by the general definition of the composition disclosed in document (1) deemed to be composed of non-homopolymeric, substantially stereoregular polymer molecules (cf. page 11, lines 14 to 15), which excludes in fact any significant presence of random sequence and, therefore, of chiral bonds.

The Board is all the more convinced that the disclosure of document (1) cannot be understood as disclosing cyclic backbone moieties joined by chiral linkages in view of the fact that it warns against the use of chiral linkage moieties which may significantly reduce the binding constant with respect to the binding constant between normal complementary polynucleotides (cf. page 4, lines 2 to 24).

The term "predominantly achiral" in this context can only be interpreted as a precautionary formulation used by the author of document (1) against any attempt by third parties to avoid infringement of its claim by relying on a cosmetic difference. It is nevertheless the case that document (1) actually does not disclose or even suggest oligonucleotides the backbone moieties of which are joined by chiral linkages.

In the Board's judgment, the Examining Division erred in considering that chiral linkages were not excluded from the teaching of document (1).

5.6 It remains to be decided whether the person skilled in the art would have been directed to replace the achiral linkages in the polymers of document (1) comprised of morpholino subunits as backbone moieties, by chiral linkages as defined in Claim 1.

5.7 Starting from document (1) properly construed, the person skilled in the art, looking for other polymers capable of sequence specific binding to a single stranded polynucleotide, comprised of morpholino subunit structures, would have considered the possibility to replace the achiral linkages disclosed in document (1) by other achiral linkages since this document warns against the use of chiral linkages (cf. page 4, lines 2 to 24).

Document (2) describes, on the one hand, one of the oligonucleotides of document (1), i.e. a morpholino subunit joined by a carbamate group, namely an achiral linkage. It is, in that respect of no more relevance than document (1). On the other hand, it mentions in the introduction part ribonucleosides or deoxyribonucleosides the phosphodiester linkage of which was replaced by methanephosphonates or phosphoramidates (cf. page 6134). However, the person skilled in the art would not have been directed to select such groups since document (1) incites him to look for other achiral linkages. Further, he would have been led to disregard this possibility because document (3) teaches that such a modification is detrimental to the stability of the formed duplex (cf. abstract).

Since no prior art directs in an obvious manner the person skilled in the art to design oligonucleotides comprised of morpholino subunits joined by phosphorous chiral linkages as defined in Claim 1, capable of sequence specific binding to a single stranded polynucleotide, the claimed subject-matter meets the requirements of Article 56 EPC. The same applies to dependent Claims 2 to 13 which represent particular embodiments of the subject-matter of Claim 1.

Claim 14 relating to a method for detecting, in a sample, the presence of a polynucleotide having a selected target sequence, involving a polymer of any of Claims 1 to 13 is based on the same inventive concept and derives its patentability on the same basis as does Claim 1. The same applies to dependent Claims 15 to 19 which represent particular embodiments of the subject-matter of Claim 14.

6. Article 111(1) EPC - Remittal to the first instance

Although the Board has come to the conclusion that the request was to be allowed, it was noted that the description has still to be put into conformity with the claims of the present request. Therefore, having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance, the Board exercises its discretion under Article 111(1) EPC to remit the case to the first instance in order for the description to be adapted to the allowable claimed subject-matter according to the request submitted before the Board at the oral

proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The matter is remitted to the first instance with the order to grant a patent on the basis of Claims 1 to 19 submitted at the oral proceedings on 11 December 2003 and a description yet to be adapted thereto.

The Registrar | The Chairman

N. Maslin | A. Nuss