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D E C I S I O N
of 21 July 1999

Case Number: T 1134/97 - 3.3.4

Application Number: 85100898.7

Publication Number: 0154788

IPC: C07H 21/00

Language of the proceedings: EN

Title of invention:
Detectable molecules, method of preparation and use

Applicant:
Enzo Biochem, Inc.

Opponent:
-

Headword:
Detectable molecules/ENZO

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
T 0021/81, T 0852/91

Catchword:
-



Case Number: T 1134/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 July 1999

Appellant: Enzo Biochem, Inc.
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New York, N.Y. 10013 (US)

Representative: Vossius & Partner
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 2 July 1997
refusing European patent application
No. 85 100 898.7 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: D. D. Harkness
W. Moser

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division dated 2 July 1997 whereby European Patent Application No. 85 100 898.7 having the title "Detectable molecules, method of preparation and use" was refused in accordance with Article 97(1) EPC.

The prior art documents cited were:

(1) EP-A-0 097 373

(2) WO-A-8 302 277

(4) EP-A-0 128 332

II. The appellant (applicant) filed a notice of appeal and paid the appeal fee on 4 September 1997. On 12 November 1997, a statement setting out the grounds of appeal was filed together with a new main request.

III. The Board issued a communication in respect of this request. The latter was subsequently replaced by a new main and one auxiliary request.

IV. At oral proceedings on 21 July 1999, the appellant withdrew all previous requests and filed a new main request and two auxiliary requests, the claims 1 of which read as follows:

Main request:

"1. A detectable molecule of the formula $A^3-(X-R^1-E-Det^b)_m$ where A^3 is A^2 , a polysaccharide, a polypeptide, a polynucleotide, or a synthetic polymer, each of said polysaccharide, polypeptide, or polynucleotide or

-Y- is a direct bond to -E-, or -Y- is -E-R²- where -R²- is a C₁-C₁₀ branched or unbranched alkylene;

Z_a is chlorine, bromine or iodine;

-E- is O, NH or an acyclic divalent sulfur atom; and

Det^b is a chemical moiety capable of being detected comprising a substituted or unsubstituted metal chelator, or a compound capable of yielding a metal chelator; and

m is an integer from 1 to the total number of modified reactive groups on A³,

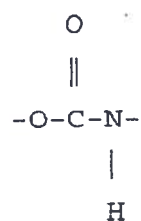
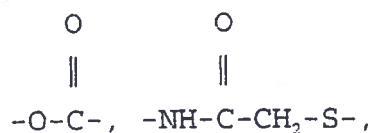
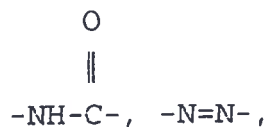
whereby a compound wherein A³ is DNA, X is -N=N-, R¹ = 1,4-(3,5-dichloro)-phenylene, Y is E-R², R² is -CH₂-CH₂-, E is -S- and Det^b is DCTA, is excluded."

Auxiliary request 1:

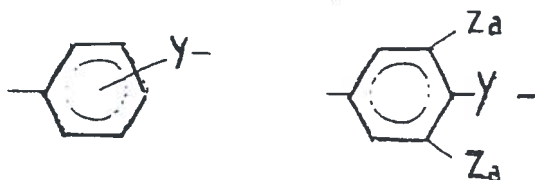
"1. A detectable molecule of the formula A³-(X-R¹-S-Det^b)_m where A³ is A², a polysaccharide, a polypeptide, a polynucleotide, each of said polysaccharide, polypeptide, or polynucleotide having at least one modifiable reactive group comprising an amino, hydroxy, 1,2-cis diOH, halide, aryl, imidazolyl, carbonyl, carboxy, thiol or a residue comprising an activated carbon;

A² is a ligand other than a polysaccharide, polypeptide, polynucleotide having at least one modifiable group and having a molecular weight of less than about 2,000;

-X- is selected from the group consisting of



-R¹- is selected from



and a C₁-C₁₀ branched or unbranched alkylene or aralkylene;

-Y- is a direct bond to -S-, or -Y- is -S-R²- where -R²- is a C₁-C₁₀ branched or unbranched alkylene;

Z_a is halogen, such as chlorine or bromine,;

Det^b is a chemical moiety capable of being detected comprising a substituted or unsubstituted metal chelator, or a compound capable of yielding a metal chelator; and

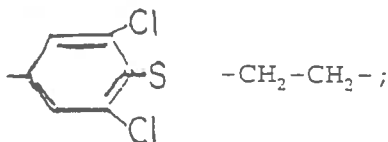
m is an integer from 1 to the total number of modified reactive groups on A³,

whereby a compound wherein A³ is DNA, X is -N=N-, R¹ = 1,4-(3,5-dichloro)-phenylene, Y is E-R², R² is -CH₂-CH₂-, E is -S- and Det³ is DCTA, is excluded."

Auxiliary request 2:

"1. Detectable molecule of the formula A³-X-R¹-S-DCTA wherein A³ is dextran with a modified OH group, X is -O-CO-NH- and R¹ is ethylene; or A³ is a protein with a modified amino group, X is -NH-CO-CH₂-S- and R¹ is ethylene; or A³ is a protein with a modified amino group, X is -NH-CO- and R¹ is ethylene; or A³ is a protein with an activated carbon on tyrosine or histidine,

X is -N=N- and R¹ is



or A³ is a protein with an activated carbon on tyrosine or histidine, X is -N=N- and R¹ is phenylene;

or A³ is a polynucleotide with a modified uridine allylamine group, X is -NH-CO- and R¹ is ethylene."

V. The submissions by the appellant can be summarised as follows:

The subject-matter of the claims of the main request and of the first auxiliary request was based on the disclosure in the application as filed on page 5 at paragraphs 2 to 4, formula VII on pages 7 and 14, and the description on page 18. The subject-matter of the

single claim of the second auxiliary request was disclosed in Table 1 on page 19 of said application. Accordingly, the requirements of Article 123(2) EPC were met as regards the claims of all requests on file.

The advantages of the claimed molecules were that they were usable in *in vivo* and *in vitro* therapeutic, diagnostic, imaging and assay techniques. The DCTA molecule could be used without having to extensively modify nucleotides and the invention provided a wide range of alternative methods utilizable in polypeptide, polynucleotide, polysaccharide and small molecule chemistry. Also the invention was more versatile than the prior art in that it was possible to provide a greater number of detectable molecule combinations. Such advantages supported the inventive step required by Article 56 EPC.

VI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the following documents, submitted during oral proceedings:

- (a) claims 1 to 15 as main request, or
- (b) claims 1 to 14 as first auxiliary request, or
- (c) claim 1 as second auxiliary request.

Reasons for the Decision

1. The appeal is admissible.
2. *All requests*

Allowability of amendments, Article 123(2) EPC

From the above section IV it is seen that claim 1 of the main and first auxiliary requests is limited to detector groups which are metal chelators or a compound capable of yielding a metal chelator and that the definitions of -E- in both requests and -X- and -Y- in the first auxiliary request have been restricted. Also the amendment to the definition of Za in the first auxiliary request to include halogen in general is supported by the description at page 15, line 4, and the amendment to claim 10 of the main request and claim 9 of the first auxiliary request to include the phrase "...carbon residue on tyrosine, histidine or guanine, inosine or cytidine.", by the description at page 18, lines 7 to 9. The subject-matter of the further claims of the main and first auxiliary requests also does not extend beyond the content of the application as filed, because no features have been added to the claims which are not supported by the description of the European patent application as filed (see formula IV on pages 7 and 14, pages 11 to 13, 15 and 18). Further, these requests represent limitations to the numbers of molecules claimed. The single claim of the second auxiliary request represents some of the molecules disclosed in Table 1 on page 19 of the description of the application as filed. Therefore the requirements of Article 123(2) EPC are met.

3. *Main request*

Novelty, Article 54 EPC

The molecules claimed have essentially three parts, (1) a basic molecule joined by (2) a chemical linking chain to (3) a moiety which is capable of being detected.

Document (1), in items 1, 77 to 80, 143 (nucleotide), 152 (polynucleotide), 169 and 170, discloses all three parts of the molecules claimed in general in the claims according to the main request, but does not provide a specific example of a molecule being the same as those claimed in any of the claims of the main request. The disclosure of particular molecules in claim 19 of document (1) relates to (1) a nucleotide joined to a diaminocyclohexanetetraacetic acid (DCTA) as detectable chelating moiety (3), whilst claim 6 refers to molecules in which a nucleotide (1) is joined by a chemical linkage (2), olefinic in claim 7 and $-\text{CH}_2-\text{NH}-$ in claim 8, to the detectable moiety (3) which are all different from those molecules claimed in the main request.

The closest disclosure in document (2) is given on page 12 where a biotin moiety (3) is joined by a link $-\text{NH}-(\text{CH}_2)_6-\text{NH}-$ (2) to a base molecule (1). However, there is no disclosure of a metal chelator (3) eg, DCTA and this prior art is thus also not novelty destroying for the subject-matter of the application according to the main request.

The disclaimer in claim 1 distinguishes the subject-matter of that claim from that of Example 1a of document (4), which is prior art under Article 54(3) EPC.

Accordingly, the subject-matter of the claims 1 to 15 of the main request is novel vis-à-vis the prior art.

4. *Inventive step, Article 56 EPC*

4.1 Closest prior art

Document (1) is considered to be closest prior art because it discloses the three features of the claimed detectable molecules in general (see paragraph 3 above).

4.2 The problem to be solved

In the light of this disclosure the problem to be solved is that of providing alternative detectable molecules.

4.3 The solution to the problem.

The problem was solved by the provision of the detectable molecules as defined in claim 1 (see section IV above).

4.4 Assessment of inventive step

The question to be answered for the determination of inventive step is whether it was obvious for the skilled person to prepare molecules as defined in claim 1.

The basic functional structure of detectable molecules is specifically disclosed in claims 6 to 8 of document (1), which structure is formed from a base molecule (1) joined via a chemical linkage (2) to a detectable moiety (3).

According to claim 1 the base molecule (1) may be *inter alia* a polynucleotide as specified in item 152 of document (1); thus, document (1) seeks to detect the same molecules as does the subject-matter of claim 1. Also document (1) discloses metal chelators, eg. DCTA, as detectable moiety (3), (see claim 19), these being the only detectable moieties disclosed in the application in suit and, thus, there is no new technique disclosed for detection purposes.

Even though the molecule (1) to be detected and made detectable in the application in suit may differ from those molecules already made detectable in the prior art by the same method, this difference is not significant because it is obvious to the skilled person that any such molecule may be linked to the detectable moiety (3) via a chemical linkage (2), because the general structure ie. (1), (2), (3), comprising a molecule (1) to be detected and which can be any basic molecule, joined via a link (2) to the detectable moiety (3), is known from items 77 to 80, 143, 152, 169 and 170 of document (1).

With regard to the chemical linkage (2) connecting the base molecule (1) and the metal chelator (3), there are many possibilities given in the application in suit, and these include those known images of a conventional nature, ie. "known intermediate linking agents" and "known linking arms", (see page 5 last paragraph and page 6 line 11 respectively of the application in suit). There is no significant difference between such known linkages and those referred to and specified in document (1) at items 77 to 80, where olefinic bonds and the bondings $-\text{CH}_2-\text{NH}-$ and $-\text{CH}=\text{CH}-\text{CH}_2-\text{NH}-$ are specified.

Therefore, the molecules claimed in the application in suit are similar in structure to those of document (1) in that they contain the same functional elements and in use are designed to operate in the same way as the prior art molecules, ie, a detectable moiety is linked to a molecule which is normally not easily detectable. Accordingly, the modus operandi of the claimed molecules is the same as that of the molecules disclosed in document (1). There admittedly are structural differences between the novel molecules of the application in suit and the prior art molecules which have been created by combining known features for (1), (2) and (3) in different combinations, but such differences do not affect their usefulness which is due solely to the presence of component parts (1), (2) and (3) (see paragraph 3 above). Therefore the differences in structure do not contribute in this case to the establishment of inventive step, (see eg Board of Appeal Decision T 852/91 of 6 June 1994).

The appellant argued that the invention was more "versatile" than the prior art. This versatility is considered to mean that many more novel molecules have been prepared and that, therefore, a larger and more varied group of molecules may be detected. But the possibility as such to prepare a larger number does not establish inventive step for the otherwise conventionally prepared functional molecules having a known or even a new linkage unless, eg, the type of linkages would be the decisive element to do so. This is not the case in the application in suit, which employs much conventional and routine chemistry but provides no unexpected advantage or effect which is not already disclosed by document (1).

Although the application in suit provides new detectable molecules, the advantage to be derived from that, ie, that they may be detected, was to be expected, because it was obvious to a skilled person that such detectable molecules would result by applying the technique of the prior art to the molecules (see eg Appeal Board Decision T 21/81 OJ 1983, 15, paragraph 6 of the reasons). An inventive step is therefore not recognised for the claimed subject-matter.

First and second auxiliary requests

5. *Novelty, Article 54 EPC*

The subject-matter of each of these requests is also novel for the reasons given in paragraph 3 above.

6. *Inventive step, Article 56 EPC*

The differences between the claims of the auxiliary requests and those according to the main request are that the claims specify preferred molecules falling within the novel group of molecules of the main request, i.e., preferred combinations of parts (1), (2) and (3). Since the individual parts (1), (2) and (3) in themselves bring no technical advantage and no advantage is obtained by combining them, the subject-matter of these claims does not differ in any way from that of claim 1 of the main request which would allow an assessment of inventive step other than that for the main request.

Therefore, the same reasons as given for the main request in paragraph 4 apply to these requests which also do not represent inventive subject-matter.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:

U. Bultmann

U. Bultmann

U. Kinkeldey

U. Kinkeldey

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