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**Datasheet for the decision
of 7 September 2006**

Case Number: T 1293/04 - 3.3.04

Application Number: 96928663.2

Publication Number: 0923601

IPC: C07K 1/04

Language of the proceedings: EN

Title of invention:

Libraries of backbone-cyclized peptidomimetics

Applicant:

PEPTOR LTD, et al

Opponent:

-

Headword:

Peptidomimetics/PEPTOR

Relevant legal provisions:

EPC Art. 56, 123(2)

Keyword:

"Added subject-matter (no)"

"Inventive step - (no)"

Decisions cited:

-

Catchword:

-



Case Number: T 1293/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 7 September 2006

Appellant:

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted 26 May 2004
refusing European application No. 96928663.2
pursuant to Article 97(1) EPC.**

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
D. Rogers

Summary of Facts and Submissions

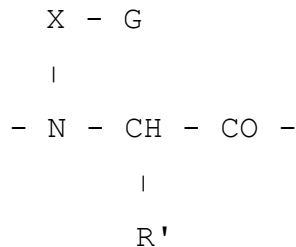
- I. The appeal was lodged by the Applicant (Appellant) against the decision of the Examining Division to refuse under Article 97(1) EPC the patent application EP 96 928 663.2, international publication number WO 97/09 344. The patent application has the title: "Libraries of backbone-cyclized peptidomimetics".
- II. The Examining Division decided that the application according to the main request and auxiliary requests 1 to 4 before them had been amended in such a way that it contained subject-matter extending beyond the application as filed, contrary to the requirements of Article 123(2) EPC.
- Moreover, they decided that the subject-matter of the claims of auxiliary request 5 before them did not involve an inventive step within the meaning of Article 56 EPC.
- III. The Board expressed its preliminary opinion in two communications dated 13 February 2006 and 10 August 2006.
- Oral proceedings were held on 7 September 2006.
- IV. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 17 of the main request dated 2 August 2006.

V. Claim 1 of this main request (the only independent claim) read:

"A method of screening for active peptide analogs comprising:

- (a) generating a library of chemical compounds;
- (b) testing members of the library for biological activity; and
- (c) identifying the active members of the library,

wherein the library of chemical compounds comprises a mixture of conformationally constrained backbone-cyclized peptide analogs, each analog comprising a peptide sequence having at least one building unit comprising an N^α-derivative of an amino acid of the general formula IV:



Formula (IV)

wherein

X is an alkylene, substituted alkylene, arylene, cycloalkylene or substituted cycloalkylene spacer group;

R' is an amino acid side chain, optionally bound with a specific protecting group; and

G is an amine, thiol, alcohol, carboxylic acid, ester or alkyl halide functional group

which is incorporated into the peptide sequence and subsequently selectively cyclized via the functional group G with one of the side chains of the amino acids in said peptide sequence or with another ω -functionalized amino acid derivative;

wherein

at least one backbone nitrogen in each said peptide sequence is linked to a side chain of at least one other amino acid in said peptide sequence or to at least one other backbone nitrogen in said peptide sequence by a bridging group comprising a disulfide, amide, thioether, thioester, imine, ether, or alkene to form a backbone-cyclized peptide analog; and

said analogues vary by both the position of the bridgeheads (i.e. the positions in the linear sequence of residues that are to be cyclized), as well as the length, the direction and the bond type of the bridge."

VI. The present decision refers to the following documents:

(2) Biopolymers, vol.31, 1991, pages 745 to 750

(5) EP-A-0 564 739

(6) J. Med. Chem., vol.37, 1994, pages 1233 to 1251

(11) Gilon C. et al; Peptide Chemistry, Yanaihara
(Ed.), 1993, Escom Scientific Publishers, Leiden
(NL), pages 482 to 485

VII. The submissions made by the Appellant as far as they
are relevant to the present decision may be summarised
as follows:

The subject-matter of claims 1 to 17 had a basis in the
application as originally filed according to the
requirements of Article 123(2) EPC. Independent claim 1
was based on claims 12 and 21 and on page 9, lines 5 to
16 of the application as originally filed.

Although the concept of backbone-cyclization was known
from prior art documents (2), (5) and (11), none of
these documents had disclosed the idea of constructing
libraries consisting of backbone-cyclized peptides for
screening purposes. At the relevant date of the present
application only random libraries were used for these
purposes. By using mixtures of conformationally
constrained backbone-cyclized peptides according to the
present invention drug discovering screening processes
could be decisively accelerated. Documents (2) and (11)
did not disclose backbone-cyclized peptide analogs as
defined in the present claims. Document (5) disclosed
one single example of a peptide analog falling within
the definition recited in claim 1. Therefore, these
prior art documents did not allow the skilled person to
arrive at the method of screening for active peptide
analogues according to claim 1 in an obvious way.

Moreover, document (6), a detailed review article
dealing with applications of combinatorial technologies

to drug discovery, contained references to 161 documents referring to the here relevant technical field. Although document (6) was published after the publication dates of documents (2), (5) and (11), none of these 161 references referred to the concept of backbone-cyclization.

Thus, claims 1 to 17 involved an inventive step (Article 56 EPC).

Reasons for the decision

Amendments - Article 123(2) EPC

1. Claim 21 as originally filed refers to a method of screening for active peptide analogs comprising, as a first step, the generation of a library of chemical compounds according to claim 12 as originally filed. Page 9, lines 5 to 16 as originally filed, describes methods for screening for bioactive conformationally constrained peptide analogs by generating a library whose individual members vary in those points described in present claim 1, screening the library for bioactivity and identifying active members of the library.

All features of claim 1 have a basis in the application as originally filed (claims 12 and 21 and page 9, lines 5 to 16). Dependent claims 2 to 17 are based on claims 2 to 4, 6 to 10 and 22 to 24 as originally filed.

Accordingly, the requirements of Article 123(2) EPC are met.

Novelty - Article 54 EPC

2. The subject-matter of claims 1 to 17 is not disclosed in the cited prior art documents. For the reasons given in points 3 to 11 below with regard to inventive step (Article 56 EPC), the Board, in the present decision, does not consider it to be necessary to give a more detailed reasoning concerning the requirements of Article 54 EPC.

Inventive step - Article 56 EPC

3. Backbone-cyclized peptides are known in the art. This is acknowledged on page 5, lines 13 to 16 of the application as filed by referring, amongst others, to documents (2) and (5).
4. Document (5) discloses peptides of the general formula (II) (see page 3 and claim 1). These peptides fall within the definition given in present claim 1 for the individual members of the library generated for the claimed method of screening for active peptide analogs. A single specific compound, designated as being a preferred peptide according to formula (II), is disclosed on page 8 of document (5) (formula (IIa)). Claim 19 of document (5) refers to a process for the preparation of peptides of general formula (II). Due to the definition given to the integers and variables contained in general formula (II) and in the formulas in claim 19, the process of claim 19 is suitable for the manufacture of peptide analogs varying in the position of the bridgeheads, as well as the length, the

direction and the bond type of the bridge, which is shown in formula (II) as a circled line.

Besides the peptides of general formula (II) document (5) also discloses peptides of general formula (I), which contain a linkage (bridge) between the N-backbone and the amino end of the peptide. In "Biological Activity Example (A)" on pages 27 to 28 of document (5), three peptides of general formula (I), namely compounds (Ia), (Ib) and (Ic), and one compound of general formula (II), namely compound (IIa), are tested for their selectivity towards tachykinin receptors in different tissues. All tested peptide analogs were highly selective to the NK-1 sub-receptor.

5. Document (2) describes the concept of backbone-cyclization for the production of conformationally constrained peptides. Figure (4) on page 748 shows the concept of N-backbone cyclization and differentiates between the possibilities of "N to N-backbone-", "N-backbone to side chain-" and "N-backbone to end-cyclization". On page 749, left column, it is reported that a series of six N-backbone to amino end cyclic analogs were synthesized and tested for their activity and selectivity to bind the NK-1 receptor. The same tests are described in document (11) (see abstract and table 1 on page 483).
6. Claim 1 of the present application refers to a method for screening a library for active peptide analogs. The library comprises a mixture of conformationally constrained peptides which are either "N to N-backbone-" or "N-backbone to side chain-cyclized"

analogs. Such peptide analogs per se are disclosed in documents (2), (5) and (11).

According to page 8, lines 33 to 35 of the application as filed, libraries in accordance with the present invention have at least four members.

According to the Appellant the term "mixture" is intended to designate a group of compounds which can be tested simultaneously by the method of claim 1. The individual members of such mixture may either be contained in one single solution or may be locally separated, as for instance at different defined positions of a microarray.

7. The problem underlying the present patent application in the light of the disclosure in documents (2) or (5), which both, individually, can be considered to represent the closest state of the art, is the provision of an alternative method for screening for active peptide analogs.

This problem is solved by the method of claim 1, which differs from the disclosure in the closest prior art in so far as a mixture (as defined in point 6 above) of at least four "N to N-backbone-" or "N-backbone to side chain-cyclized" peptide analogs are tested, whilst document (2) tests a series of six "N-backbone to amino end-cyclized" peptide analogs and document (5) tests three "N-backbone to amino end-cyclized" and one "N to N-backbone-cyclized" peptide analogs.

8. The question to be answered is whether or not the skilled person trying to solve the posed problem,

having regard to the state of the art, would have arrived at the claimed subject-matter in an obvious way.

9. Document (2) discloses in figure (4) on page 748 the concept of N-backbone cyclization and describes three different cyclization models for the manufacture of conformationally constrained peptides, namely "N to N-backbone-", "N-backbone to side chain-" and "N-backbone to end-cyclization".

In the same way document (5) contains detailed information concerning the concept of N-backbone cyclization for the manufacture of conformationally constrained peptides and discloses "N-backbone to side chain-" and "N-backbone to end-cyclization" (formulas (I) and (II)).

Thus, a skilled person trying to solve the underlying problem and to provide an alternative to the screening method disclosed in either of documents (2) or (5), would find the solution according to claim 1 in exactly these documents.

10. The Applicant argued that, at the relevant date of the present application, only random libraries had been used for screening purposes. The use of libraries of conformationally constrained compounds for this purpose had not, at that time, been taken into consideration by the experts in this technical field. The concept of backbone-cyclization has not been mentioned in any of the 161 references indicated in document (6), a detailed review article dealing with applications of combinatorial technologies to drug discovery.

In the light of the disclosure in documents (2) and (5), as discussed above, this argument must fail. Moreover, document (6) explicitly refers to two different ways of carrying out the combinatorial discovery exercise (page 1234, right column, first full paragraph). One being random screening with the task to identify a lead compound in the absence of any structural information about active molecules, the other being **directed screening** or **chemical analoging** in order to evaluate closely related structural analogs of a lead molecule.

There may be many reasons why document (6) does not refer to the concept of backbone-cyclization. However, backbone-cyclization is disclosed in documents (2), (5) and (11), these documents forming part of the state of the art, and, for the reasons outlined in points (3) to (9) above, based on these documents a person skilled in the art would arrive at the claimed subject-matter in an obvious way. The non-referral to backbone-cyclization in document (6) cannot negate the disclosure in documents (2), (5) and (11) and thus cannot form a basis for a finding of inventive activity.

11. The Board therefore concludes that the subject-matter of claim 1 does not involve an inventive step as required by Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar:

Chair:

P. Cremona

U. Kinkeldey