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**Datasheet for the decision
of 9 November 2006**

Case Number: T 0641/05 - 3.3.08

Application Number: 00982220.6

Publication Number: 1238076

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:

G protein-coupled receptor-like receptors and modulators thereof

Applicant:

Pharmacia & Upjohn Company LLC

Opponent:

-

Headword:

GPCR-like receptor/PHARMACIA

Relevant legal provisions:

EPC Art. 57

EPC R. 27(1)(f)

Keyword:

"Industrial application (no) - computer-assisted method lacking probative value"

Decisions cited:

T 0870/04, T 0898/05

Catchword:

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Case Number: T 0641/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 9 November 2006

Appellant: Pharmacia & Upjohn Company LLC
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Kalamazoo, MI 49001 (US)

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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 3 January 2005
refusing European application No. 00982220.6
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Rennie-Smith

Summary of Facts and Submissions

- I. European patent application number 00 982 220.6 (published as WO 01/38533 with the title "G protein-coupled receptor-like receptors and modulators thereof") was refused by the examining division pursuant to Article 97(1) EPC.
- II. The examining division considered that the main request (filed on 2 September 2002) and auxiliary requests 1 to 4 (filed on 15 November 2004) did not fulfil the requirements of Article 56 EPC. The main request was also considered to contravene Article 84 EPC in combination with Article 83 EPC.
- III. The applicant (appellant) lodged an appeal against the decision of the examining division. With the statement setting out the grounds of appeal, the main request was withdrawn and auxiliary requests 1 to 4 were refiled.
- IV. The examining division did not rectify its decision and, pursuant to Article 109(2) EPC, remitted the appeal to the Boards of Appeal.
- V. By letter of 12 July 2006, the appellant was summoned to oral proceedings on 9 November 2006. In a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal ("RPBA") sent with the summons, the board expressed its provisional opinion on the issues of Article 56 EPC and reference was also made to Articles 57 and 83 EPC. The board referred to two review articles (cf. section XII *infra*, documents A and B) that were annexed to the communication.

- VI. On 22 September 2006, the board drew the attention of the appellant to decision T 898/05 of 7 July 2006 in relation to issues under Article 57 EPC.
- VII. With letter dated 18 October 2006, the appellant withdrew the request for oral proceedings and informed the board of its intention not to attend oral proceedings in case that they were not cancelled.
- VIII. In a telefax communication dated 31 October 2006, the appellant was informed of the board's provisional opinion that none of the requests on file complied with Article 57 EPC. Oral proceedings were maintained as scheduled and the appellant was further informed that a decision was expected to be announced at the end of oral proceedings.
- IX. On 9 November 2006, oral proceedings took place in the absence of the appellant.
- X. Independent claims 1, 20 and 21 of **auxiliary request 1** read on file as follows:
- "1. A method of identifying a modulator of an activity of a GPCR-like receptor, comprising the following steps:
- (a) contacting a test compound with a composition which comprises an invertebrate GPCR-like receptor selected from polypeptides encoded by a polynucleotide having SEQ ID NO: 1 or a polynucleotide hybridising thereto under stringent conditions of hybridising at 42°C in a solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate, and washing twice for 30 minutes

at 60°C in a wash solution comprising 0.1 X SSC and 1% SDS; and

(b) measuring the activity of the GPCR-like receptor in the presence and absence of the test compound."

"20. An isolated GPCR-like receptor comprising SEQ ID NO: 2."

"21. An isolated polynucleotide encoding a GPCR-like receptor, comprising a sequence encoding a polypeptide according to claim 20, e.g. SEQ ID NO: 1."

Claims 2 to 10 concerned further embodiments of claim 1, in particular, claim 4 referred to several assays (ion flux, yeast growth, non-hydrolysable GTP, etc.), claim 5 to different G-proteins ($G_{\alpha 16}$, $G_{\alpha 15}$, $G_{\alpha d5}$, etc.), claim 7 to GPCR-like receptors encoded by specific SEQ ID NO and claim 8 to peptides of specific SEQ ID NO. Claims 11 to 13 concerned methods of identifying a candidate anti-invertebrate modulator or agent and claims 14 to 19 concerned methods of detecting an invertebrate GPCR-like receptor. Claims 22 to 25 were particular embodiments of claim 21 (vectors and host cells transformed or transfected therewith).

XI. **Auxiliary request 2** was identical to auxiliary request 1 except for the deletion of claims 14 to 19. **Auxiliary requests 3 and 4** only comprised, respectively, claims 1 to 19 and 1 to 13 of auxiliary request 1.

XII. The following documents are cited in the present decision:

A: J. Wess, *Pharmacol. Ther.*, Vol. 80, No. 3, pages 231 to 264, 1998;

B: G.J. Kilpatrick et al., *Trends in Pharmacol. Sci. (TIPS)*, Vol. 20, pages 294 to 301, July 1999.

D4: J. Nelson et al., *Database EMBL*, accession no.: Q22876, 1 June 1998 (as cited in the decision under appeal. However, the accession number is from the Swiss-Prot database).

XIII. Although the decision under appeal did not refer to Article 57 EPC, the statement setting out the grounds of appeal explicitly referred thereto. The appellant's arguments in writing, insofar as they are relevant to the present decision, may be summarized as follows:

The general disclosure of the application

The application disclosed the nucleotide and amino acid sequences of the CEGPCR1 from *Caenorhabditis elegans* (SEQ ID NO: 1, 2), a member of the superfamily of G protein-coupled receptors (GPCRs). CEGPCR1, a splice variant of the AC7.1 polypeptide disclosed in document D4 differed from AC7.1 by 31 amino acids, which resulted in a truncated second extracellular domain. These different structures of the second extracellular domain could be responsible for a difference in the ligand-binding profile exhibited by both receptors. CEGPCR1 was identified as falling into a group of neuropeptide receptors specific to invertebrates and

closely related to the vertebrate family of neurokinin receptors. This identification was based on bioinformatics analyses with six other neuropeptide receptors disclosed in the application and it had been confirmed with the sequences of other neuropeptide receptors known from the prior art. The application provided thus a targetable receptor suitable for selectively interfering vital neuromuscular activities of (pest) invertebrates while being less likely to interfere with (non-pest) plants and animals as well as a method for identifying modulators of neuropeptide receptors preferentially functional in (pest) invertebrates but not in vertebrates.

Industrial applicability

CEGPCR1 shared 89.6% amino acid sequence identity with AC7.1, a (rhodopsin) GPCR-like receptor disclosed in document D4. This degree of homology supported the same applications of AC7.1 for the claimed CEGPCR1, including antibody and ligand binding as well as a mediation of signal transduction characteristic of AC7.1 and other GPCRs. In fact, GPCRs were known to be involved in signal transduction pathways that mediated many medically significant biological processes and therefore, they were recognised as important therapeutic targets for a wide range of diseases. Genes encoding GPCRs were used *inter alia* in toxicological tests for generating information useful for drug development, even in cases where little was known as to how a particular GPCR worked. Because GPCRs, as a class, conveyed practical and specific benefits, the identification of GPCRs was recognised as a task of prime importance in itself and there was no need to

provide additional information. Commercial products related to GPCRs for which no function had been identified were also commercially available. At least three companies made and sold those products proving thereby that there was a well-established industrial application for GPCRs as a class. Several patents had also been granted by the US Patent and Trademark Office (USPTO) to GPCRs and related products (polynucleotides and antibodies) for which no natural substrate or specific biological significance was known. Nevertheless, a credible, substantial and specific utility had been acknowledged for all these GPCRs.

Article 57 EPC only excluded a research tool from patentability when its use was the sole subject of the research itself. However, this was not the case for GPCRs or for the related CEGPCR1 disclosed in the application, since CEGPCR1 could be used to identify binding ligands, protein-binding partners and/or modulators, to generate antibodies for localizing CEGPCR1 *in vivo* or *in vitro* as well as for determining the expression pattern of the CEGPCR1 gene in various tissues.

The present application demonstrated a substantial likelihood of industrial application by showing a reasonable correlation between the utility of the known GPCRs and the claimed related GPCR-like receptor CEGPCR1. The assertions made in the application for industrial applicability were thus believable to the skilled person based on the totality of the evidence and the (sound scientific logic) reasoning provided. They were not flawed nor were the facts upon which they

were based logically inconsistent and no evidence had been provided to the contrary.

- XIV. The applicant (appellant) had requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of any of the auxiliary requests 1 to 4 which were filed with the statement of grounds of appeal.

Reasons for the Decision

Article 57 EPC and the case law of the Boards of Appeal relating to biological substances

1. For a European patent to be granted, an invention has to satisfy *inter alia* the requirement of being "*susceptible of industrial application*" (Article 52(1) EPC), a requirement which is fulfilled if the invention "*can be made or used in any kind of industry, including agriculture*" (Article 57 EPC). In this respect, Rule 27(1)(f) EPC prescribes that the description should "*indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is capable of exploitation in industry*".

2. In line with the broad interpretation of the notion of "*industry*" established by the case law (cf. "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, I.E.1, page 141), decision T 898/05 of 7 July 2006 interpreted a "*profitable use*" - as referred to in decision T 870/04 of 11 May 2005 (cf. point 4 of the Reasons) - in a wide sense and it further stated that

"a claimed invention must have such a sound and concrete technical basis that the skilled person can recognise that its contribution to the art could lead to practical exploitation in industry, i.e. to a **concrete benefit**, which is **immediately** derivable directly from the description, if it is not already obvious from the nature of the invention or from the background art. It is necessary to disclose in definite technical terms the purpose of the invention and how it can be used in industrial practice to solve a given technical problem, this being the actual concrete benefit or advantage of exploiting the invention."
(emphasis added) (cf. T 898/05, *supra*, points 4 to 6 of the Reasons).

3. In decision T 870/04 (*supra*), a distinction was made between i) cases where, in addition to the structure of a substance, its function is also elucidated or it is already known from the art, and ii) cases where a substance is identified, and possibly also characterised, but either its function is not known or it is complex and incompletely understood and there is no disease or condition attributable to an excess or deficiency of this substance. In cases falling under i) a practical industrial application of the substance in question can in general be easily seen and, if so, Article 57 EPC is fulfilled, whilst in cases falling under ii) if no practical application can be envisaged, industrial applicability cannot be acknowledged (cf. points 5 and 6 of the Reasons).
4. In decision T 898/05 (*supra*), the function of a protein was defined at different levels and it was acknowledged that the elucidation of one of these particular levels

might result, under certain conditions, in a straightforward industrial application (cf. points 29 and 30 of the Reasons). The decision further stated that the probative value of a function based on computer-assisted methods, rather than on the basis of traditional wet-lab techniques, has to be examined on a case-by-case basis regarding the nature of the invention and the prior art relating thereto (cf. point 22 of the Reasons).

The general disclosure of the application

5. The present application identifies several putative G protein-coupled receptor (GPCR)-like receptors from the invertebrate (nematode, roundworm) *Caenorhabditis elegans*. Some of these GPCR-like receptors, namely clones CEGPCR3, CEGPCR4, CEGPCR5, CEGPCR7, CEGPCR12c, CEGPCR12h, CEGPCR12u, CEGPCR12v, CEGPCR16, CEGPCR19.1 and CEGPCR19.2, are shown - by a [³⁵S]GTP γ S binding assay - to bind to one or more neuropeptide ligands and thus, to be neuropeptide receptors (cf. page 53, line 7 to page 61, line 4, Tables 7 to 13 of the published application). By a bioinformatics method using release 23 of the Wormpep database (which contains all of the predicted protein sequences encoded by the *C. elegans* genome), these receptors are identified in a **first tier** of receptors which also comprises clones CEGPCR11, CEGPCR13, CEGPCR14 and CEGPCR17 (cf. page 69, lines 12 to 20).

6. Clones CEGPCR1a, CEGPCR1f, CEGPCR3, CEGPCR15, CEGPCR18A, CEGPCR20 and CEGPCR25 are identified - by the same bioinformatics method - as "(a)n additional group of receptors (falling) into a **second tier**"

(emphasis added) (cf. page 69, lines 20 to 22). By comparison of their sequences with the GenBank database, the components of this second group of clones are identified as *"also likely peptide receptors, although they have not yet been matched to ligands"* (cf. page 69, lines 22 to 24). This second tier of *C. elegans* receptors is described as tending *"to fall into classes with other known neuropeptide receptors"*, in particular clones CEGPCR1 and CEGPCR24 *"fall into an interesting group (that) contains only invertebrate receptors, but is most closely related to the vertebrate family of neurokinin (NK-1,2,3) receptors"* (cf. page 70, lines 9 to 20 and page 72, line 30 to page 73, line 3).

The specific disclosure of the CEGPCR1a clone (SEQ ID NO: 1, 2)

7. Clones CEGPCR1a (SEQ ID No.: 1) and CEGPCR1f (SEQ ID No.: 3) are identified in the application as *"each showing some sequence similarity to Wormpep AC7.1"*, which is taken as the reference sequence for these two clones (cf. page 14, Table 1 and page 32, lines 20 to 21). The hypothetical AC7.1 protein encoded by *C. elegans* cosmid AC7 is disclosed in the prior art document D4 - with a cross-reference to the InterPro database (*"Integrated resource of protein families, domains and functional sites"*) from the European Bioinformatics Institute (ebi) - as a putative member of the rhodopsin-like GPCR superfamily. The application defines clones CEGPCR1a and CEGPCR1f as splice isoforms of CEGPCR1, since they both differ from the CEGPCR1 sequence by a deletion of 94 bp (corresponding to a deletion of 31 amino acid residues in the second extracellular (2EC) domain) and by, for clone CEGPCR1f only, an insertion of 45 bp (corresponding to 15

additional amino acid residues in the third cytoplasmic (3IC) domain) (cf. page 14, Table 1).

8. However, clones CEGPCR1a and CEGPCR1f are explicitly defined as being only "**initial clones**", since the alignment of their sequences "*suggested that other variant clones might also exist that contained an initiator ATG in a **more conventional** location than within the first transmembrane region*" (emphasis added) (cf. page 68, lines 18 to 24). In fact, both clones comprise two initiator ATG codons within the disclosed open reading frame (at positions 151-153 and 175-177) and two other ATG codons within different open reading frames (at positions 144-146 and 158-160), all of them within the first transmembrane region (1TM). The application also refers to a further "**unusual feature**", namely the presence of "*a few atypical amino acids in the conserved "DRY" motif immediately following 3TM, e.g., "HEF" in the CEGPCR1a and CEGPCR1f sequences*" (emphasis added) (cf. page 69, lines 29 to 31). At the priority date of the present application (24 November 1999), it was well known in the prior art that the "DRY" motif - in particular the arginine (R) - was highly conserved in most (99%) receptors of the rhodopsin-type receptor family and that it was critical for the function of these GPCR-like receptors, since its absence or replacement abolished or drastically reduced the G-protein coupling (cf. document A, point 7.4.1 on pages 245 and 246).

9. The application further refers to subsequent releases of the Wormpep database which "*included a longer AC7.1 sequence corresponding to CEGPCR1 (but still not the splice variants)*" and to the design of a new primer

based on this longer sequence. Using this new primer "**additional clones** were isolated" (emphasis added) (cf. page 68, lines 24 to 29). However, the sequences of these additional clones are not disclosed in the application and there is no information concerning these additional clones, such as their structural relationship with the "initial clone" CEGPCR1a, the presence or absence of more conventional initiator ATG codons and/or of the highly conserved "DRY" motif.

10. Based only on sequence homology analyses, CEGPCR1 is also described as "*tending to fall*" into a group of known invertebrate neuropeptide receptors which is "*closely related*" to a vertebrate family of receptors (cf. point 6 *supra*). However, there is no further indication as to the nature or character of this tendency and relatedness, such as the degree of homology, the presence or absence of conserved structural motifs and/or of important fingerprints within these neuropeptide receptors and, most important, no distinction is made between the reference CEGPCR1 (AC7.1) sequence and the specific sequence of the splice variant CEGPCR1a or the other undisclosed "*additional clones*" (cf. point 9 *supra*).

11. Nevertheless, at the priority date of the application, it was already known that GCPR splice variants could have very different properties, such as in their specificity and/or efficiency for ligand binding and/or in the G-protein coupling, with consequent effects on the signalling transduction pathways used by these splicing variants. In fact, these differences are shown in the application itself with respect to the splice variants CEGPCR19.1 (SEQ ID NO: 107) and CEGPCR19.2

(SEQ ID NO: 105) (cf. pages 60 and 61, Tables 12 and 13), whereas none is reported for the related splice variants CEGPCR12c, CEGPCR12u and CEGPCR12v of the CEGPCR12h receptor (cf. page 58, lines 13 to 19 and page 59, Table 11). Moreover, it was also known in the art that some GPCR splice variants had no activity at all, i.e. they were non-functional showing no ligand binding and/or no G-protein coupling, whereas other splice variants resulted from a "*leaky transcription*" and were thus physiologically irrelevant (cf. document B).

Conclusion

12. In view of the foregoing considerations, the board concludes that, although the CEGPCR1a clone - defined in the application as a splice variant of CEGPCR1 (AC7.1) - has some structural features of a GPCR-like receptor, it also presents some other non-conventional and unusual features. Consequently, it is classified in the application itself as an "*initial clone*" only, with reference to other undisclosed "*additional clones*" (cf. point 9 *supra*). In the light of the prior art and in the absence of any actual functional characterization of the disclosed CEGPCR1a clone, it is mere speculation to draw any conclusions from the deletion of 31 amino acid residues in the 2EC domain of CEGPCR1 (AC7.1) (whether the ligand binding specificity and/or efficiency is only modified, partially inhibited or completely abolished) and the absence of the highly conserved "DRY" motif (whether or not a G-protein coupling is present at all). This is even more so since the reference CEGPCR1 (AC7.1) (putative) protein has

- also been characterized only by sequence homology comparison.
13. Therefore, the board considers that no actual information regarding the function of the CEGPCR1a clone - at any of the three particular levels of function referred to in decision T 898/05 (*supra*, points 29 and 30 of the Reasons), i.e. molecular, cellular and biological function in a broad sense (binding of a ligand, propagation of a transmembrane signal, role in a transduction signal pathway and/or in a network of interconnected pathways of a multicellular organism) - can be directly derivable from the application itself or from the prior art on file. Nor has the appellant provided any evidence in that respect in reply to the board's concerns expressed in the communication under Article 11(1) RPBA and in a later telefax communication (cf. sections V and VIII *supra*).
14. Although, under certain conditions, the board is well prepared - following the case-by-case approach adopted in decision T 898/05 (*supra*) - to acknowledge a possible function based on computer-assisted methods (cf. point 4 *supra*), in the present case the probative value of these (sequence homology) methods is completely lacking for the reasons set out above. In the absence of this functional information, the CEGPCR1a clone disclosed in the present application can only be equated or put on a par with the second group of cases identified in decision T 870/04 (cf. point 3 *supra*), namely those cases for which no industrial application, i.e. no "*immediate concrete benefit*" in the sense defined in decision T 898/05 (cf. point 2 *supra*), can be recognized.

15. Since all the requests on file are based on the disclosed clone CEGPCR1a (SEQ ID NO: 1 and 2), none of them is considered to fulfil the requirements of Article 57 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani