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D E C I S I O N
of 12 January 2006

Case Number: T 0362/04 - 3.3.04

Application Number: 97948309.6

Publication Number: 0941113

IPC: A61K 38/18

Language of the proceedings: EN

Title of invention:

Methods and compositions for stimulating neurite growth using compounds with affinity for FKBP12 in combination with neurotrophic factors

Applicant:

VERTEX PHARMACEUTICALS INCORPORATED

Opponent:

-

Headword:

Stimulation of neurite growth/VERTEX

Relevant legal provisions:

EPC Art. 56, 113(1), 116(1)

RPBA Art. 11(3)

Keyword:

"Inventive Step - no"

Decisions cited:

T 0091/98, T 0748/01

Catchword:

-



Case Number: T 0362/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 12 January 2006

Appellant: VERTEX PHARMACEUTICALS INCORPORATED
130 Waverly Street
Cambridge, MA 02139-4242 (US)

Representative: Vossius & Partner
Siebertstrasse 4
D-81675 München (DE)

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 6 October 2003
refusing European application No. 97948309.6
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: R. Moufang
Members: G. Alt
R. Gramaglia

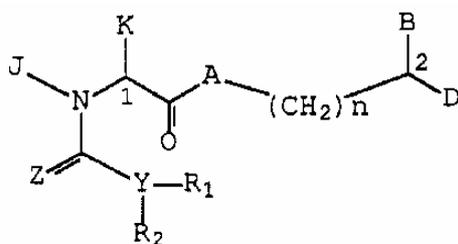
Summary of Facts and Submissions

I. The appeal was lodged by the applicant against the decision of the examining division to refuse the European patent application No. 97 948 309 with the title "Methods and compositions for stimulating neurite growth using compounds with affinity for FKBP12 in combination with neurotrophic factors" pursuant to Article 97(1) EPC because the subject-matter of claim 1 lacked an inventive step.

II. Claim 1 on which the decision under appeal is based read:

"1. A pharmaceutically acceptable composition comprising:

a) a neurotrophic amount of a compound having the formula (I):



Formula (I)

and pharmaceutically acceptable derivatives thereof, wherein:

A is CH₂, oxygen, or NR₁;

wherein R₁, B and D are independently:

hydrogen, Ar, (C1-C6) straight or branched alkyl, (C2-C6) straight or branched alkenyl or alkynyl, (C5-C7) cycloalkyl substituted (C1-C6) straight or branched

alkyl, (C5-C7) cycloalkyl substituted (C3-C6) straight or branched alkenyl or alkynyl, (C5-C7) cycloalkenyl substituted (C1-C6) straight or branched alkyl, (C5-C7) cycloalkenyl substituted (C3-C6) straight or branched alkenyl or alkynyl, Ar-substituted (C1-C6) straight or branched alkyl, or Ar-substituted (C3-C6) straight or branched alkenyl or alkynyl;

wherein any one of the CH₂ groups of said alkyl chain in R1, B and D is optionally replaced by O, S, SO, SO₂ or NR;

wherein R is hydrogen, (C1-C4) straight or branched alkyl, (C3-C4) straight or branched alkenyl or alkynyl, or (C1-C4) bridging-alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl chain to form a ring, and wherein said ring is optionally fused to Ar;

J is selected from hydrogen, (C1-C6)-straight or branched alkyl, (C3-C6)-straight or branched alkenyl, or -CH₂Ar;

K is selected from (C1-C4)-straight or branched alkyl, -CH₂Ar, or cyclohexylmethyl; or

J and K are taken together with the nitrogen and carbon atoms to which they are respectively bound to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from O, S, SO and SO₂;

Z is O or S;

Y is O or N; wherein

when Y is O, then R₁ is a lone pair and R₂ is selected from Ar, (C1-C6)-straight or branched alkyl, and (C3-C6)-straight or branched alkenyl or alkynyl; and when Y is N, then R₁ and R₂ are independently selected from the group consisting of Ar, (C1-C6)-straight or branched alkyl, and (C3-C6)-straight or branched alkenyl or alkynyl; or R₁ and R₂ are taken together to form a heterocyclic 5-6 membered ring selected from the group consisting of pyrrolidine, imidazolidine, pyrazolidine, piperidine, and piperazine;

wherein Ar is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl;

wherein Ar is optionally substituted with one to three substituents which are independently selected from hydrogen, halogen, hydroxyl, nitro, -SO₃H, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or

branched alkyl, (C2-C6)-straight or branched alkenyl, O [(C1-C6)-straight or branched alkyl], O-[(C3-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2 methylenedioxy, -NR₃R₄, carboxyl, N-(C1-C5-straight or branched alkyl or C3-C5-straight or branched alkenyl) carboxamide, N,N-di-(C1-C5-straight or branched alkyl or C3-C5-straight or branched alkenyl) carboxamide, morpholinyl, piperidinyl, O-Z, CH₂-(CH₂)_q-Z, O-(CH₂)_q-Z, (CH₂)_q-Z-O-Z, or CH=CH-Z;

wherein R₃ and R₄ are independently selected from (C1-C6)-straight or branched alkyl, (C3-C6) straight or branched alkenyl or alkynyl, hydrogen or benzyl; or wherein R₃ and R₄ are taken together to form a 5-6 membered heterocyclic ring;

wherein Z is selected from 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazolyl, isoxazolyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, or pyrimidyl;

wherein q is 0-2; and

n is 0 or 1;

b) a neurotrophic factor; and

c) a pharmaceutically suitable carrier.

III. With the statement of grounds of appeal the applicant filed two documents (hereinafter numbered as D3 and D4) to support its case. Grant of a patent was requested on the basis of the set of claims under consideration in

- the decision under appeal. Oral proceedings were requested as an auxiliary measure.
- IV. Oral proceedings were summoned.
- V. In a further communication dated 5 January 2006 the applicant informed the board that it withdrew the request for oral proceedings and asked for "a written decision based on the records".
- VI. The board informed the appellant that oral proceedings would take place as scheduled.
- VII. Oral proceedings were held on 12 January 2006 in the absence of the appellant.
- VIII. The following documents are mentioned in this decision:
- D1: ZA 96/04852
- D2: WO 95/26337
- D3: Lyons, W.E. et al., Proc. Natl. Acad. Sci., USA, vol. 91, pages 3191 to 3195, April 1994, "Immunosuppressant FK506 promotes neurite outgrowth in cultures of PC12 cells and sensory ganglia"
- D4: WO 99/10340
- IX. The appellant's arguments submitted in writing as far as they are relevant for the present case can be summarised as follows:

Document D1 disclosed only that the two classes of compounds mentioned in the document possessed neurotrophic activity as well as affinity for FKBP12. This was no evidence that neurotrophic activity and affinity for FKBP12 were always linked.

Indeed, at the priority date of the application the relationship between FKBP12 binding and neurotrophic activity was not well understood as shown by document D3. The authors of that document speculated that the neurotrophic effects of FK-506, a compound binding to FKBP12, were exerted by acting through FKBP12 to inhibit calcineurin (page 3194, right column, lines 6-15). An alternate hypothesis involved FK506 acting at the ryanodine receptor (page 3195, left column, lines 13-18). Additionally the authors speculated that further mechanisms not involving FKBP12 may play a role (page 3195, left column, lines 18-22).

Post-published evidence, document D4, demonstrated that there were compounds that did not bind to FKBP12, but nevertheless stimulated neurite outgrowth.

Therefore, the skilled person either would have not turned to FKBP12-binding compounds when searching for compounds with neurite growth promoting activity or, even if he had assayed FKBP12 binding compounds for neurotrophic activity, had no reasonable expectation of success that they had the desired activity because such an activity could not be predicted with a sufficient degree of certainty.

The compounds disclosed in document D1 were structurally different from those of the present

application. There was no pointer in document D1 to focus on such structurally dissimilar compounds.

The compounds of the present application were structurally disclosed in document D2. As to their function document D2 disclosed however only that they were useful for sensitizing cells against multi-drug resistance, a physiological situation which was totally unrelated to the neurological degeneration disorders.

Reasons for the Decision

Procedural matters

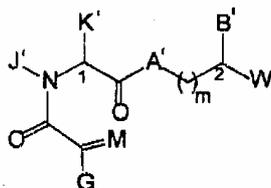
1. The holding of oral proceedings does not only serve the purpose of giving a party a fair chance to argue its case in accordance with Article 113(1) and 116(1) EPC, first sentence, second alternative. It also enhances procedural efficiency since it makes it possible that the board reaches its decision as quickly as possible. This is supported by Article 116(1) EPC, first sentence, first alternative, according to which oral proceedings shall take place if the board considers this to be expedient. In the present case, notwithstanding the appellant's withdrawal of its request for oral proceedings, the Board has therefore refrained from cancelling the scheduled oral proceedings. As made clear in Article 11(3) of the Rules of Procedure of the Boards of Appeal, a party duly summoned to oral proceedings and not attending may be treated as relying only on its written case. The Board furthermore notes that the appellant, in its last communication,

expressly asked for a "written decision on the records". Thus, Article 113(1) EPC has been satisfied.

Inventive step - Article 56 EPC

2. The only substantive issue dealt with in the decision under appeal and also in this decision is that of inventive step.
3. Document D1, a published patent application, is the closest prior art document. It discloses compositions comprising
 - (a) a neurotrophic amount of a compound with affinity for FKBP12 being of a general formula (I) or (II)
 - (b) a neurotrophic factor and
 - (c) a pharmaceutically suitable carrier.

The backbone of the compounds having formula (II) is as follows:



The document has three examples. Example 1 describes an FKBP12-binding assay and gives on pages 22 to 30 data on the FKBP12-binding activity of compounds falling under the general formulae. Examples 2 and 3 describe two different assays to determine neurite outgrowth. It is concluded at the end of both examples that "the FKBP binding compounds utilised in this invention cause a significant increase in neurite outgrowth over control cultures", without giving any experimental data.

4. The subject-matter of document D1 is a composition comprising, like the composition of the application, a neurotrophic factor and a pharmaceutically suitable carrier. The difference between the two compositions lies in that the compounds of the present invention are esters or amides (Y is oxygen or nitrogen, respectively in formula (I) of present claim 1). In contrast, the compounds of formula (II) of document D1 contain at the equivalent position either a dicarbonyl [-C(=O)-C(=O)] moiety or a [-C(=O)-C(=CH-U')(G)-] moiety (when M is oxygen or CH-U', respectively).

5. The present application has twenty four examples. Twenty three of them deal with the preparation of twenty three compounds falling under the general formula of part (a) of claim 1. Example 24 describes an assay to determine neurite outgrowth which is the same as that of example 2 of document D1. Without giving experimental data on the growth it is concluded at the end of the example that "the compounds described in this invention herein cause a significant increase in neurite outgrowth over background control cultures."

6. Whether in the absence of data and in view of the many compounds encompassed by the general formula of part (a) of claim 1 it can be considered credible that the twenty three prepared compounds or even all compounds falling under the terms of claim 1 indeed possess this property, has not been an issue in the decision under appeal. In the absence of evidence to the contrary the board assumes for the purposes of the present reasoning that, as claimed by the applicant (the appellant), all

compounds encompassed by claim 1 have the indicated activity.

Hence, the problem underlying the claimed invention is the provision of a further composition comprising chemical compounds, which in the presence of a neurotrophic factor and a pharmaceutically suitable carrier stimulate neurite outgrowth.

7. The question to be answered for the evaluation of inventive step is whether the skilled person starting from document D1 is led in an obvious manner by document D1 or other prior art documents on file to solve the problem by choosing the compounds of formula (I) of claim 1.

8. As noted in point 3 above, document D1 reports experimental data about FKBP12-binding and states at the end of Examples 2 and 3 that "the FKBP binding compounds utilised in this invention cause a significant increase in neurite outgrowth over control cultures". Moreover, when formulating the problem underlying the invention disclosed in document D1, it is stated: "There remains a great need for additional **neurotrophic FKBP12-binding** compounds." (emphasis added). In view of this disclosure and given the fact that the document contains detailed data about FKBP12-affinity, but none about nerve growth activity, the skilled person would understand that there was a relationship between FKBP12-binding and neurotrophic activity and would assume that FKBP12-binding activity was a good indicator for nerve growth activity.

9. Moreover, document D1 has to be seen in connection with document D3, published in April 1994, i.e. more than 2 years before the publication of document D1. Document D3 is individually cited in these proceedings. It is also cited and its contents are discussed on pages 2 and 3 of document D1 (see in point 12 below).

Document D3 discloses that FK506, an FKBP12-binding compound which was originally discovered as an immunosuppressant drug, stimulates neurite outgrowth. In the light of this result it is stated on page 3194 that "it is tempting to speculate that **FK506 acting through FKBP12** inhibits calcineurin to increase levels of phosphorylated calcineurin substrates." (emphasis added). Thus, document D1 is not the first document reporting a relationship between neurite growth and FKBP12-binding, rather it takes up the teaching of document D3 and confirms it.

10. Thus, the board considers that document D1 conveyed to the skilled person the clear teaching that there was a link between FKBP12-binding and neurite outgrowth stimulating activity.
11. The appellant's argument that this link had not been clearly established at the priority date of the present application, is not convincing. It is true that the authors of document D3 speculate also about other, FKBP-12 independent pathways for stimulation of neurite outgrowth. However, even if their existence had not been demonstrated, they were thought to be present in addition to the FKBP-12 dependent mechanism: "**In addition** FK506 acts on other sites, including FKBP-25, steroid receptors, and other unidentified targets such

as those related to FKBP13. Thus, other mechanisms may play some role in neurite extension." (page 3195; emphasis added).

12. As noted above, the contents of document D3 are discussed in the introduction of document D1. This passage of document D1 may be regarded as an indication of how the skilled person interpreted the teachings of document D3 in June 1995, i.e., before the priority date of the present application. In this passage the authors only allude to the FKBP12-dependent mechanism, but not to the other possible mechanisms suggested in document D3. Moreover, the involvement of FKBP12 in neurite growth seemed no longer to be treated as speculative because the authors of document D1 state (page 2, lines 31-32): "Another role of FKBP12 is the regulation of neurite outgrowth of nerve cells." Thus, the board considers that a skilled person had even already inferred from the teachings of document D3 that FKBP12-binding and neurite growth activity were related, an inference which was confirmed by the teachings of document D1.
13. Later evidence such as that of document D4, disclosing compounds binding to FKBP12, but not having neurotrophic activity, does not reflect the skilled person's view at the priority date, and thus cannot be taken into account.
14. Thus, in the board's view, the skilled person wishing to solve the problem as stated in point 6 above would have investigated FKBP12-binding compounds for neurotrophic activity with one of the known tests as described, for example, in document D1.

15. Therefore, the skilled person would have turned to the compounds disclosed in document D2 which, apart from their usefulness for resensitisation of multidrug resistant cells or for prevention of multidrug resistance, were known to bind FKBP12. This is because it is stated on page 14 of document D2 that:

"According to one embodiment of this invention, compounds that are useful in increasing, restoring or maintaining drug sensitivity are also capable of binding to the protein FKBP-12 or other related FK-506 binding proteins such as FKBP-13, FKBP-26 and FKBP-52. In vitro tests (data not shown) of these compounds demonstrate that the agents bind to FKBP-12."

16. The compounds covered by the general formula in document D2 fall under the terms of the general formula of part (a) of claim 1 of the present application. In passing it is noted that the subject-matter of claim 1 is not anticipated by that of document D2 because the latter does not disclose the compounds in a composition with a neurotrophic factor.

17. Consequently, in the board's judgement, the skilled person when trying to solve the problem formulated in point 6 above would have been led in an obvious manner by a combination of the teachings of documents D1 and D2 to replace the compounds of formula (II) of claim 1 of document D1 with the compounds disclosed in document D2 and would thus have arrived at subject-matter embraced by the terms of claim 1 of the application.

18. The appellant's argument that the skilled person would not have chosen the compounds of document D2 because their neurotrophic activity could not be predicted, thus lowering the expectation of success, is not convincing.

19. In the board's view, there is no question of reasonable expectation of success here. This concept was developed in cases where subject-matter could easily be conceived theoretically, but where its realisation caused problems and was therefore not of a routine nature. Therefore, overcoming them and being able to produce said subject-matter may justify acknowledgment of inventive step. In the present case however, the testing of compounds which are already hinted at in the prior art may be laborious, but is nevertheless routine work and can therefore not support inventive step (see for example T 91/98 of 29 May 2001, point 8 of the Reasons; T 748/01 of 16 February 2005, point 19 of the Reasons).

20. Thus, the subject-matter of Claim 1 does not fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar:

Chair:

P. Cremona

R. Moufang