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D E C I S I O N
of 15 April 1997

Case Number: W 0006/96 - 3.3.1

Application Number: 95936273.2

Publication Number: W09611931

IPC: C07D 471/04

Language of the proceedings: EN

Title of invention:
Polycyclic fused ring modulators of acetylcholine receptors

Applicant:
Sibia Neurosciences, Inc.

Opponent:
-

Headword:
Modulators of Acetylcholine Receptors/SIBIA

Relevant legal provisions:
PCT Art. 34(3)(a)
PCT R. 68.3, 13.1, 13.2
PCT Guidelines for International Preliminary Examination, chapter C-III, 7.6

Keyword:
"Unity of invention (yes) - common new activity - benefit of the doubt"

Decisions cited:
W 0004/96

Catchword:
-

Case Number: W 0006/96 - 3.3.1
International Application No. PCT/US95/12905

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 15 April 1997

Applicant: Sibia Neurosciences, Inc.
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Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicant against the invitation (payment of additional fee) of the European Patent Office (International Preliminary Examining Authority) dated 10 July 1996.**

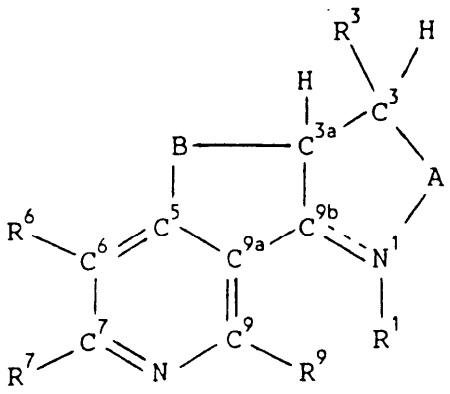
Composition of the Board:

Chairman: A. Nuss
Members: P. Spangenberg
R. Teschemacher

Summary of Facts and Submissions

I. International patent application PCT/US 95/12905, concerning polycyclic fused ring modulators of acetylcholine receptors, was filed on 28 September 1995. An International Search Report was established by the EPO for all 31 claims of this patent application. Claim 1 reads as follows:

"1. A compound having the structure:



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wherein:

A is a 1, 2 or 3 atom bridging species which forms part of a 5-, 6- or 7-membered ring including N^1, C^{9b}, C^{3a} and C^3; and
B is a 1, 2 or 3 atom bridging species which forms part of a 5-, 6- or 7-membered ring including C^5, C^{9a}, C^{9b} and c^{3a}; and
R^1 is selected from hydrogen, lower alkyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, or R^1 is absent when there is a double bond between N^1 and C^{9b}; and
R^3 is selected from hydrogen or a lower alkyl moiety; and
R^6 and R^7 are independently selected from hydrogen, alkyl,

substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, aroyl, substituted aroyl, heteroaryl, substituted heteroaryl, acyl, halogen, trifluoromethyl, trialkylsilyl, triarylsilyl, cyano, nitro, -S(O)-R' -$S(O)_2$-R', -$S(O)_2$-NHR', -C(O)-NHR' or -NH-C(O)-R', wherein each R' is lower alkyl or aryl; -OR", -$NR"_2$ or - SR" , wherein each R" is independently selected from hydrogen, lower alkyl, aryl, substituted aryl, alkylaryl or substituted alkylaryl; and R^9 is selected from hydrogen or lower alkyl; with the proviso that, when A is -CH_2-, B is -CH_2CH_2-, and each of R^3, R^6, R^7, and R^9 are -H, then R^1 is not -H or -CH_3.

II. On 9 May 1996 a demand for international preliminary examination was received. On 10 July 1996 the European Patent Office, as competent International Preliminary Examining Authority (IPEA), issued an invitation to restrict the claims or to pay four additional fees in accordance with Article 34(3)(a) and Rule 68.2 PCT.

The IPEA considered that the application did not comply with the requirement of unity of invention as set forth in Rule 13 PCT and indicated that J. Med. Chem. 1993, 36, pages 3381 to 3385 (henceforth referred to as D1) disclosed modulators of acetylcholine receptors, in particular compounds 7 and 8 of D1, which compounds had been excluded from the scope of product claim 1, pharmaceutical composition claim 17 and medicinal use claim 18 by means of a proviso.

Starting from D1, the problem underlying the application was seen in the provision of further compounds that are modulators of acetylcholine receptors, i.e. that are

capable of displacing one or more acetylcholine receptor ligands, e.g. ^{3}H-nicotine, from mammalian cerebral membrane binding sites. The IPEA considered that this problem had been solved by different technical means which had nothing inventive in common.

III. The Applicant paid three additional fees under protest in accordance with Rule 68.3(c) PCT. He submitted that the IPEA had not properly applied the "Markush practice" according to the Administrative Instructions under the PCT. He pointed out that, as required by that practice, all alternatives presented in claim 1 possessed the common property or activity to be capable of selectively modulating the activity of acetylcholine receptors. Further on, these compounds also shared at least one significant structural element, i.e. the identical "basis element" A being $-CH_2-$. In addition, the "structural element" B was very similar, namely being $-CH_2CH_2-$ in Groups (1) to (3) and OCH_2 in Group (4), while R^1 was ethyl or methyl, two substituents being in close technical relationship, thus forming a common inventive concept.

IV. After having performed the review pursuant to Rule 68.3(e), the review panel of the IPEA confirmed that the objection re lack of unity was justified for the reasons as set forth in the invitation to pay the additional fees, and invited the applicant to pay the protest fee. After payment of this fee the protest was referred to the Board of Appeal for examination in accordance with Rule 68.3(c) PCT.

Reasons for the Decision

1. The communication containing the result of the prior review and inviting the Applicant to pay the protest fee does not

reveal the composition of the review panel. Implementing Rule 68.3(e) PCT, the President of the EPO has prescribed the composition of the body responsible for carrying out the prior review (OJ EPO 1992, 547). On enquiry with the IPEA, the Board received from their file internal notes signed by the three members of the review panel, indicating the result of their meeting and referring to the reasons annexed to the invitation to pay the protest fee. On this basis the Board is satisfied that the composition of the review panel and the invitation to pay the protest fee was correct.

2. The protest is admissible.

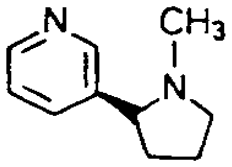
3. The objection of lack of unity of invention was raised by the IPEA a posteriori, i.e. taking into account the state of the art (see point II above). According to Part 1(f)(v) of Annex B to the Administrative Instructions under the PCT (published in the PCT Gazette of May 30, 1996 (No. 24/1996, page 9474), which is referred to in the Guidelines for International Preliminary Examination to be carried out under the Patent Cooperation Treaty, Chapter III, 7.5), and is therefore binding for the EPO acting as an IPEA (cf. the decision G 1/89 of 2 May 1990, OJ EPO 1991, 155), the question of unity of invention may be reconsidered if it can be shown that at least one Markush alternative is not novel over the prior art. In the Board's judgment, the fact that in the present case the two known alternatives were not claimed, because they were excluded by a proviso, does not change the situation, since according to Rule 13.1 PCT the relevant question is not whether or not the applicant knew the state of the art when drafting his claims, but only whether or not the above-identified inventions are so linked as to form a single general inventive concept. The IPEA was thus entitled to reconsider the question of

unity of invention in the present case, once it had become clear that the proviso in Claim 1 of the present international patent application excluded compounds belonging to the state of the art.

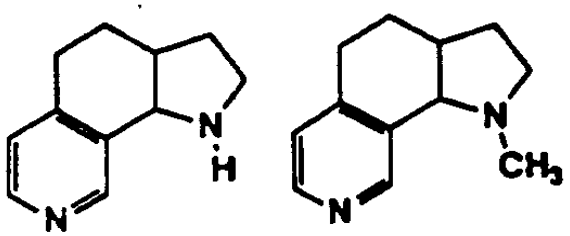
4. Contrary to the Applicant's submission, in the Board's judgment the above-mentioned Administrative Instructions should **not** be interpreted to mean that a Markush group of chemical compounds sharing a common **known** property or activity, in a case where all significant structural elements shared by all of the alternatives are also known, nevertheless belong to one single inventive concept. On the contrary, it follows from Rule 13.2 PCT, setting out the circumstances in which the requirement of unity of invention shall be fulfilled, that a group of inventions claimed in the same international application can only form a single general **inventive** concept within the terms of Rule 13.1 PCT when there is a technical relationship among those inventions involving one or more of the same or corresponding **special** technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes **over** the prior art. This means, that either a common structural or functional technical feature must be present which does not yet belong to or is rendered obvious by the state of the art (see also W 4/96 - 3.3.2 of 20 December 1996, to be published in the OJ EPO).

5. The Board is, however, not satisfied that indeed the relevant activities or properties disclosed in the present international patent application as being common to all compounds of formula I (see point I above) are indeed known or rendered obvious by the disclosure of D1. This document is a scientific paper concerning the characterization of

different sub-types of the so-called "nicotinic" acetylcholine receptor (see page 3381, "Introduction").



For this purpose derivatives of nicotine of formula namely compounds of formulas **7** and **8** have been synthesized and tested.



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The results of these tests were commented as follows (see page 3383, left column, second complete paragraph, emphasis added):

"**These pharmacological data are intriguing** for several reasons. First, preparation of conformationally restricted analogs resulted in compounds with **relatively low affinity for the nicotine receptor**. Even the compound [(+/-)-7] with the highest affinity was 100 times less potent than nicotine, and **(+)-8 was completely devoid of affinity** for the nicotine receptor. Yet, (+)-8 exhibited pharmacological properties and potencies similar to those of nicotine. It is a well-established fact that mecamylamine is capable of blocking almost all of the centrally mediated effects of nicotine and all other agents

that bind to the nicotinic receptor. The failure of mecamylamine to antagonize the effects of (+)-8 provides further support that this analog is **not binding to the nicotine receptor**. One plausible explanation for these findings is that (+)-8 is producing nicotinic effects by acting at a nicotinic receptor that is not mecamylamine sensitive. **On the other hand, it is not unreasonble to conclude that these bridged analogs are not nicotine-like because they are unable to bind to the nicotine site and are not blocked by mecamylamine. Considerable pharmacological experimentation will be required to answer these questions.**"

In this situation, the Board is unable to concur with the finding in the invitation to pay additional fees that the compounds disclosed in D1 were **known** to have the property or activity of "modulating the activity of acetylcholin receptors", as set out in the present international patent application. Rather it follows from the above-mentioned test results that the said activity is not clearly and unambiguously established for the two known compounds. Moreover, according to the description of the present international patent application, page 27, line 15 to page 28, line 9, the phrase "modulating the activity of acetylcholin receptors" refers to a variety of therapeutic applications, including the treatment of Alzheimer's disease and other types of dementia. Only one of these therapeutic applications, namely the control of disorders of nociception and of pain is mentioned in D1. In view of this, there is no evidence that the claimed chemical compounds do not share a common **new** property or activity, hence a common new special (functional) technical feature.

The Board further considers that the above-mentioned Guidelines for International Preliminary Examination to be carried out under the Patent Cooperation Treaty, Chapter III-7.6 expressly state that, although lack of unity of invention should certainly be raised in **clear** cases, it should neither be raised nor persisted with on the basis of a narrow, literal or academic approach. Moreover, the benefit of any doubt should be given to the Applicant.

6. In the present circumstances, therefore, where at least reasonable doubts exist about the presence of a common new activity, the Board holds that in view of the said Guidelines an objection of lack of unity of invention is not justified.

Order

For these reasons it is decided that:

Reimbursement of the additional fees and of the protest fee is ordered.

The Registrar: The Chairman:

E.Görgmaier A.Nuss