

**Internal distribution code:**

- (A)  Publication in OJ  
(B)  To Chairmen and Members  
(C)  To Chairmen  
(D)  No distribution

**D E C I S I O N**  
**of 26 April 2005**

**Case Number:** T 0359/01 - 3.3.1

**Application Number:** 93914148.7

**Publication Number:** 0644877

**IPC:** C07D 221/18

**Language of the proceedings:** EN

**Title of invention:**

Substituted-hexahydrobenzo[a]phenanthridines

**Applicant:**

PURDUE RESEARCH FOUNDATION, et al

**Opponent:**

-

**Headword:**

Hexahydrobenzo[a]phenanthridines/PURDUE

**Relevant legal provisions:**

EPC Art. 54, 56

**Keyword:**

"Novelty (yes) - multiple selection"

"Inventive step (yes) - non-obvious alternatives"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0359/01 - 3.3.1

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.1  
of 26 April 2005

**Appellant:** PURDUE RESEARCH FOUNDATION  
1650 Engineering Administration Building  
Room 328  
West Lafayette, IN 47907-1650 (US)

**Representative:** Bannerman, David Gardner  
Withers & Rogers LLP  
Goldings House  
2 Hays Lane  
London SE1 2HW (GB)

**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 2 October 2000  
refusing European application No. 93914148.7  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

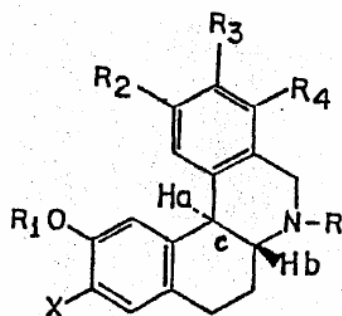
**Chairman:** A. J. Nuss  
**Members:** J. M. Jonk  
S. C. Perryman

## Summary of Facts and Submissions

- I. This appeal lies from the decision of the Examining Division refusing the present European patent application 93 914 148.7 (published under number WO 93/24462) relating to "substituted hexahydrobenzo[a]phenanthridines".
- II. The application in suit was refused on the ground that the subject-matter of the set of Claims 1 and 2 filed on 14 January 2000 lacked inventive step in view of documents:
- (A) US-A-5 047 536, and
- (B) WO 92/04356.
- III. The Examining Division held that the subject-matter of said set of claims was supported by the application as filed within the meaning of Article 123(2) EPC and also that it was novel. However, it refused the patent application on the ground that the subject-matter of Claim 1 relating to 35 particular substituted hexahydrobenzo[a]phenanthridines, which were disclosed in the description of the present application as filed, lacked inventive step in view of documents (A) and (B).
- IV. Oral proceedings before the Board were held on 26 April 2005.
- V. The Appellant defended the patentability of the subject-matter of the present application on the basis of a main request and two auxiliary requests all submitted on 29 March 2005 by facsimile.

Claim 1 of the main request read as follows:

"A compound having the formula:



and pharmaceutically acceptable salts thereof, wherein:

X is a group of formula  $-OR_5$

R is hydrogen or  $C_1-C_4$  alkyl

$R_1$  and  $R_5$  are independently hydrogen or a phenoxy protecting group selected from methyl, isopropyl, t-butyl, cyclopropylmethyl, cyclohexyl, allyl, methoxymethyl, methoxy-ethoxymethyl, methylthiomethyl, tetrahydropyranyl, benzyl, o-nitrobenzyl, p-methoxybenzyl, 9-anthrylmethyl, 4-picolyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, acetyl, propionyl, n-butyryl, isobutyryl, trimethylacetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, 2-trimethylsilylethyloxycarbonyl, vinyloxycarbonyl, benzyloxycarbonyl, methylaminocarbonyl, isobutylaminocarbonyl, phenylaminocarbonyl, benzylaminocarbonyl, and dimethylaminocarbonyl, or  $R_1$  and  $R_5$  together form a group of the formula  $-CH_2-$ ; and  $R_2$ ,  $R_3$  and  $R_4$  are independently selected from hydrogen,  $C_1-C_4$  alkyl, phenyl, fluoro, chloro, bromo, iodo, or a group  $-OR_1$  wherein  $R_1$  is as defined above,

provided that at least one of  $R_2$ ,  $R_3$  and  $R_4$  is other than hydrogen".

He argued in particular that the claimed invention related to a new class of 2, 3 and/or 4-substituted trans-hexahydrobenzo[a]-phenanthridines substituted hexahydrobenzo[a]phenanthridines of the general formula indicated in present Claim 1 of the application in suit, wherein the substituents  $R_2$ ,  $R_3$  and  $R_4$  are all hydrogen. Document (A) related to D-1 and D-2 agonists, but it contained no suggestion of substituents at the carbon atoms 2, 3 and 4. Furthermore, document (B) only concerned compounds suitable as D-1 antagonists. He concluded that under these circumstances the cited documents (A) and (B), alone or in combination, did not give any incentive to the skilled person to provide the compounds of the present claims having the demonstrated beneficial agonist properties.

VI. The Appellant requested that the decision under appeal be set aside, and that a patent be granted on the basis of the claims of the main request, or of the first or second auxiliary request, all submitted on 29 March 2005 by facsimile.

VII. At the conclusion of the oral proceedings the Board's decision was pronounced.

### **Reasons for the Decision**

1. The appeal is admissible.

2. *Amendments (Article 123(2) EPC)*

2.1 Present claim 1 is supported by claim 1 of the application as filed in combination with the description as filed, page 4, line 23 to page 5, line 8.

Claims 2 to 7 correspond to claims 2 to 7 of the application as filed.

Claims 8 to 10 correspond to claims 14 to 16 of the application as filed.

Claim 11 corresponds to claim 18 of the application as filed.

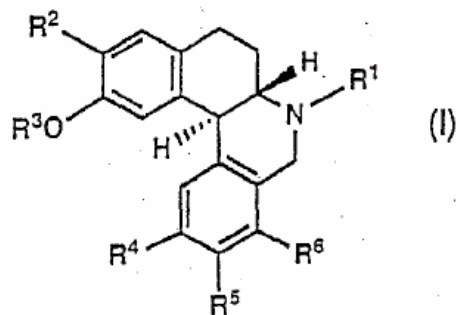
2.2 Therefore, the Board concludes that the subject-matter of claim 1 of the present main request does not extend beyond the content of the application as filed, and consequently meets the requirement of Article 123(2) EPC.

3. *Novelty*

3.1 Document (A) discloses substituted hexahydrobenzo[a]phenanthridines of a general formula corresponding to the formula indicated in present claim 1 of the application in suit, wherein the substituents  $R_2$ ,  $R_3$  and  $R_4$  are all hydrogen (see document (A), column 2, lines 20 to 46), whereas according to present claim 1 of the application in suit at least one of  $R_2$ ,  $R_3$  and  $R_4$  is other than hydrogen.

3.2 Document (B) discloses substituted hexahydrobenzo[a]phenanthridines of the formula (I) and

their isomeric forms (see page 4, second paragraph, to page 5, second paragraph; and page 11, first paragraph):



wherein:

R<sup>1</sup> (R in present claim 1)

is selected from **hydrogen, methyl, ethyl** and a prodrug amide group;

R<sup>2</sup> (X in present claim 1)

is selected from the group consisting of hydrogen, halogen, lower alkyl, **lower alkoxy**, halo-substituted lower alkyl, lower alkylthio, nitro, acetamino and -SO<sub>2</sub>R<sup>7</sup> wherein R<sup>7</sup> is lower alkyl;

R<sup>3</sup> (R<sub>1</sub> in present claim 1)

is selected from **hydrogen and a prodrug ester group**; and

R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> (R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> in present claim 1)

are independently selected from the group consisting of **hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy**, halo-substituted lower alkyl,

lower alkylthio, nitro, amino, acetamino, aminomethyl and  $-SO_2R^8$  wherein  $R^8$  is lower alkyl.

(emphasis in bold added by the Board)

Thus, in order to arrive at compounds falling under the scope of present claim 1 of the application in suit, the skilled person would have to make multiple selections from the compounds as defined in document (B) by formula (I), namely:

- (a) a selection of  $R^1$  (R in present claim 1) as hydrogen, methyl or ethyl;
- (b) a selection of  $R^2$  (X in present claim 1) as a methoxy, isopropoxy or t-butoxy group;
- (c) a selection of  $R^3$  ( $R_1$  in present claim 1) as hydrogen or particular prodrug ester groups;
- (d) a selection of  $R^4$ ,  $R^5$  and  $R^6$  ( $R_2$ ,  $R_3$  and  $R_4$  in present claim 1) independently as hydrogen, hydroxyl, halogen, lower alkyl or lower alkoxy with the provision that at least one of  $R^4$ ,  $R^5$  and  $R^6$  is other than hydrogen.

In these circumstances, and also because (i) none of the numerous exemplified compounds mentioned on pages 6 to 10 and in the Examples 1 to 63 on pages 25 to 34 of document (B) contains an alkoxy group at the 10-position as  $R^2$  (X in present claim 1), and (ii) the preferred compounds of document (B) are those in which  $R^4$ ,  $R^5$  and  $R^6$  ( $R_2$ ,  $R_3$  and  $R_4$  in present claim 1) are hydrogen (see page 10, last two paragraphs), there is



no direct and unambiguous disclosure in prior art document (B) of compounds or a group of compounds falling under the scope of present claim 1 of the application in suit.

3.3 Having regard to these considerations, the Board concludes that the claimed subject-matter is novel.

4. *Inventive step*

For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which essentially involves identifying the closest prior art, determining in the light thereof the technical problem which the claimed invention addresses and successfully solves, and examining whether or not the claimed solution to this problem is obvious for the skilled person in view of the state of the art.

4.1 The Board considers, in agreement with the Appellant, that the closest prior art with respect to the subject-matter of claim 1 of the application in suit is the disclosure of document (A).

4.2 Document (A) discloses, as indicated above under point 3.1, a group of substituted hexahydrobenzo[a]phenanthridines of a general formula corresponding to the formula indicated in present claim 1 of the application in suit, wherein however the substituents  $R_2$ ,  $R_3$  and  $R_4$  are all hydrogen. Moreover, it discloses that the compounds of this group having a 10,11-dioxy substitution pattern, like those of the application in suit, possess D-1 agonist activity (see

column 3, lines 15 to 33, of (A) and page 2, lines 9 to 15, of the application in suit).

4.3 Having regard to the Appellant's submissions, the Board accepts that the technical problem underlying the application in suit in the light of said closest prior art consists in providing further hexahydrobenzo[a]phenanthridine compounds having D-1 agonist activity and varying D2/D1 selectivity (see also page 2, line 15 to page 3, line 9; and page 18, line 24 to page 19, line 11, of the application in suit).

4.4 As the solution to this problem, the present application proposes the group of compounds according to present claim 1, which compounds are particularly characterised in that  $R_2$ ,  $R_3$  and  $R_4$  independently are selected from the substituents defined in claim 1, whereby at least one of  $R_2$ ,  $R_3$  and  $R_4$  is other than hydrogen.

Having regard to the test results indicated in the application in suit on page 18, line 24 to page 19, line 11, as well as in the statement of Richard Mailman filed on 29 December 1998, the alleged activity has been successfully demonstrated and is credible for the whole scope of present claim 1.

4.5 Finally, it remains to be decided whether or not the proposed solution to the problem underlying the application in suit is obvious in view of the cited prior art, i.e. documents (A) and (B).

- 4.6 Although document (A), as indicated above under point 4.2, discloses a group of compounds having, like the compounds of the application in suit, D-1 agonist activity, it cannot render the claimed subject-matter obvious, since it does not give any incentive to the skilled person that further hexahydrobenzo[a]phenanthridine compounds having D-1 agonist activity could be provided by introducing at least one substituent  $R_2$ ,  $R_3$  and/or  $R_4$  as defined in present claim 1 of the application in suit.
- 4.7 Document (B) discloses, as indicated above under point 3.2, a large group of hexahydrobenzo[a]phenanthridines, which partly overlaps with the group of compounds defined in present claim 1 of the application in suit. However this document only aims at providing compounds having a D-1 antagonist activity (see page 6, first paragraph; and page 36, last paragraph to page 37), i.e. a dopamine receptor blocking activity instead of a dopamine receptor stimulating activity aimed at according to the application in suit. Therefore, the skilled person would ignore the technical teaching of this document when trying to solve the problem underlying the application in suit.
- 4.8 Therefore, documents (A) and (B), alone or in combination, do not provide a pointer to the skilled person to arrive at the claimed solution of the above defined technical problem underlying the application in suit.
- 4.9 In conclusion, the Board finds that the subject-matter of present Claim 1 involves an inventive step in the sense of Article 56 EPC.

Moreover, the subject-matter of present claims 2 to 10 relating to preferred compounds, and that of claim 11 relating to a pharmaceutical composition comprising a compound of claim 1 and an inert carrier, also involve an inventive step for the same reasons.

5. *Auxiliary requests*

Since the subject-matter of the claims of the present main request meets the requirements of the EPC for the reasons set out above, there is no need for the Board to decide on the auxiliary requests.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the first instance for further prosecution on the basis of the main request submitted on 29 March 2005 by facsimile.

The Registrar:

The Chairman:

N. Maslin

A. Nuss