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DECISION
of 28 October 2004

Case Number: T 0276/00 - 3.3.1

Application Number: 93910521.9

Publication Number: 0640082

IPC: C07D 453/02

Language of the proceedings: EN

Title of invention:

Heteroaromatic quinuclidinenes, their use and preparation

Applicant:

Pfizer Health AB

Opponent:

-

Headword:

Quinuclidinenes/PFIZER

Relevant legal provisions:

EPC Art. 56, 111(1)

Keyword:

"Inventive step (yes) - non-obvious alternative compounds"
"Remittal to the first instance"

Decisions cited:

-

Catchword:

-



Case Number: T 0276/00 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 28 October 2004

Appellant:

Pfizer Health AB
S-112 87 Stockholm (SE)

Representative:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 13 September 1999
refusing European application No. 93910521.9
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman:

A. J. Nuss

Members:

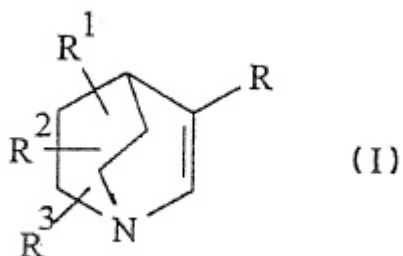
J. M. Jonk

S. C. Perryman

Summary of Facts and Submissions

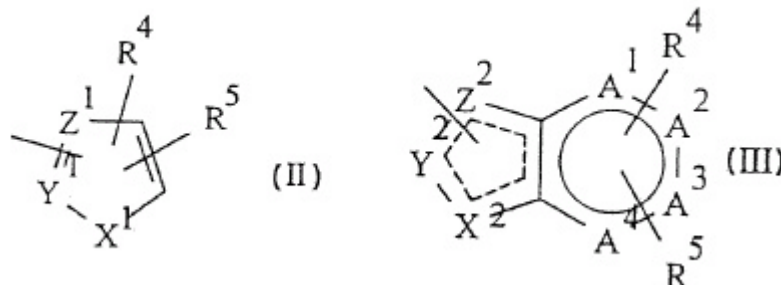
- I. This appeal lies from the decision of the Examining Division refusing the present European patent application 93 910 521.9 (published under number WO 93/23395) relating to "Heteroaromatic quinuclidinenes, their use and preparation".
- II. The Examining Division refused the application on the ground that the subject-matter of Claim 1 of the set of Claims 1-13 filed on 19 January 1999 lacked inventive step in view of documents
- (3) EP-A-0 316 718,
- (4) EP-A-0 328 200, and
- (5) EP-A-0 450 345.
- III. Claim 1 of said set of claims read as follows:

"A compound of the general Formula I:



wherein

R is a group of the general Formula II or III:



where

X^1 represents oxygen or sulphur and Y^1 and Z^1 both represent carbon;

one of X^2 , Y^2 and Z^2 represents oxygen or sulphur and either (i) the other two both represent carbon, or (ii) one represents nitrogen and the other represents carbon, and the dotted line in formula III represents an optional additional carbon-carbon or carbon-nitrogen bond;

A^1 , A^2 , A^3 and A^4 each represent carbon;

R^1 , R^2 and R^3 independently represent hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkylalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyloxy, C_{4-10} cycloalkylalkoxy, hydroxy or hydroxy- C_{1-10} alkyl; and

R^4 and R^5 independently represent hydrogen, C_{1-10} alkyl, halogen or $(CH_m)_nB$, wherein $(CH_m)_n$, in which n is an integer 0 to 10 and m independently is an integer 0 to 2, represents a bond or a straight or branched, saturated or unsaturated hydrocarbon chain and B represents phenyl or heteroaryl, each of which may be substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen, and wherein heteroaryl is selected from thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole,

triazole, pyridine, pyrazine, pyrimidine, pyridazine, benzofuran, isobenzofuran, benzothiazole, benzothiophene, indole, isoindole, oxadiazole and benzoxazole groups; COR^6 , COOR^6 , $\text{CON}(\text{R}^6)_2$, $\text{N}(\text{R}^6)_2$, OR^6 , CN , NO_2 , $\text{C}=\text{NOR}^6$, OCOR^6 , $\text{N}(\text{R}^6)\text{COR}^6$, $\text{C}(\text{R}^6)_2\text{OR}^6$, $\text{OCOC}(\text{OH})(\text{R}^6)_2$ or trifluoromethyl, where R^6 independently represents hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl or $(\text{CH}_2)_n\text{Ar}$, wherein Ar is phenyl or heteroaryl as defined above and n is as defined above;

with the proviso that when R represents a group of Formula II and R^1 , R^2 and R^3 each are hydrogen, then R is other than 2-furyl, 4-methyl-2-furyl and 5-methyl-2-furyl; and physiologically acceptable salts thereof."

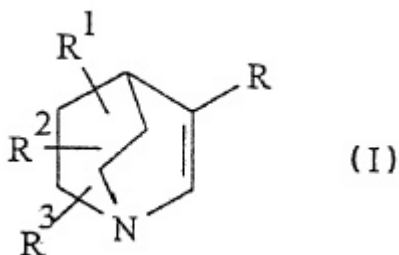
IV. The Examining Division held that the subject-matter of said set of claims was supported by the application as filed within the meaning of Article 123(2) EPC and also that it was novel. However, it refused the patent application on the ground that the subject-matter of Claim 1 specified above lacked inventive step in view of documents (3), (4) and (5). In this context, it held in particular that the subject-matter of said Claim 1 represented a novel section from the group of compounds disclosed in document (4), that the claimed compounds with $\text{R} = \text{Formula II}$ were obvious in the light of document (4) alone or in combination with document (3), and that the claimed compounds with $\text{R} = \text{Formula III}$ should be seen as further obvious alternatives of the document (5) compounds, optionally in combination with document (4).

V. Oral proceedings before the Board were held on 28 October 2004.

VI. The Appellant defended the patentability of the subject-matter of the present application on the basis of a main request and three auxiliary requests all submitted on 24 January 2000.

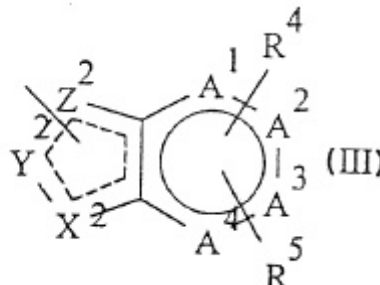
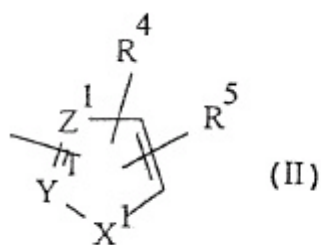
Claim 1 of the present main request, which was further restricted with respect to Claim 1 forming the basis of the decision of the Examining Division by deleting "heteroaryl" (including its indicated representatives) as a meaning of "B" and by restricting the rest "(CH₂)_nAr" concerning the meaning of "R⁶" to "phenyl", so that the claimed subject-matter did not overlap anymore with that of document (4), read as follows:

"A compound of the general Formula I:



wherein

R is a group of the general Formula II or III:



where

X¹ represents oxygen or sulphur and Y¹ and Z¹ both represent carbon;

one of X^2 , Y^2 and Z^2 represents oxygen or sulphur and either (i) the other two both represent carbon, or (ii) one represents nitrogen and the other represents carbon, and the dotted line in formula III represents an optional additional carbon-carbon or carbon-nitrogen bond;

A^1 , A^2 , A^3 and A^4 each represent carbon;

R^1 , R^2 and R^3 independently represent hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkylalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyloxy, C_{4-10} cycloalkylalkoxy, hydroxy or hydroxy- C_{1-10} alkyl; and

R^4 and R^5 independently represent hydrogen, C_{1-10} alkyl, halogen or $(CH_m)_nB$, wherein $(CH_m)_n$, in which n is an integer 0 to 10 and m independently is an integer 0 to 2, represents a bond or a straight or branched, saturated or unsaturated hydrocarbon chain and B represents phenyl, which may be substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen, COR^6 , $COOR^6$, $CON(R^6)_2$, $N(R^6)_2$, OR^6 , CN , NO_2 , $C=NOR^6$, $OCOR^6$, $N(R^6)COR^6$, $C(R^6)_2OR^6$, $OCOC(OH)(R^6)_2$ or trifluoromethyl, where R^6 independently represents hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl or phenyl;

with the proviso that when R represents a group of Formula II and R^1 , R^2 and R^3 each are hydrogen, then R is other than 2-furyl, 4-methyl-2-furyl and 5-methyl-2-furyl; and physiologically acceptable salts thereof."

He argued in particular that the cited documents, 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 pharmacological activity.

- VII. 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 one of auxiliary requests I, II or III all filed on 24 January 2004.
- VIII. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Amendments (Article 123(2) EPC)*
- 2.1 The Board concurs with the Examining Division that the subject-matter of Claim 1 forming the basis of its decision does not extend beyond the content of the application as filed.
- 2.2 Furthermore, the amendments of this claim by deleting "heteroaryl" (including its indicated representatives) as a meaning of "B" and by restricting the rest "(CH₂)_nAr" concerning the meaning of "R⁶" to "phenyl" leading to the subject-matter of present Claim 1 of this request are supported by the application as filed, in particular Claim 1; page 6, lines 37 and 38, concerning the restriction of "(CH₂)_nAr" to "phenyl"; and page 7, lines 7 to 9, with respect to the indicated substituents of said phenyl group.

2.3 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 too, and consequently meets the requirement of Article 123(2) EPC.

3. *Inventive step*

3.1 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.

If the technical results of the claimed invention provide some improvement over the closest prior art, the problem can be seen as providing such improvement, provided this improvement necessarily results from the claimed features for all that is claimed. If, however, there is no improvement, but the means of implementation are merely different, the technical problem can be defined as the provision of an alternative to the closest prior art.

3.2 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 (3).

3.3 This document discloses azacyclic compounds, such as 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2,3-didehydroquinuclidine oxalate, having muscarinic cholinergic activity and being useful in the treatment of Alzheimer's disease (see page 3, lines 1 to 16; page 3, line 22 to page 4, line 26; and Example 4).

3.4 In the light of this closest state of the art and in the absence of evidence for any improvement over this prior art, the technical problem underlying the application in suit can only be seen in the provision of alternative quinuclidinene derivatives, which block or stimulate muscarinic acetylcholine receptors, and therefore are of potential use for the treatment of diseases where cholinergic receptors are involved (see also page 3, lines 8 to 13, of the application in suit).

3.5 The present patent application suggests as the solution to this problem a class of substituted quinuclidinene compounds of Formula I as defined in Claim 1, in which R represents an optionally substituted furyl, thienyl, benzofuryl, benzothienyl, benzoxazolyl or benzthiazolyl group.

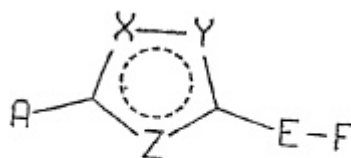
3.6 The remaining question is thus whether the prior art as a whole has suggested to a person skilled in the art solving the technical problem indicated in point 3.4 above in the proposed way.

3.7 In challenging the inventive step, the Examining Division only relied on documents (3), (4) and (5).

3.8 However, document (3) cannot render the claimed subject-matter obvious by itself, since it only

discloses quinuclidine or quinuclidinene derivatives having the indicated pharmacological activity, in which a substituent comparable to R in the compounds of the present application can be a 5-membered heterocyclic ring selected from an optionally substituted oxadiazolyl or oxazolyl group (see page 3, line 22 to page 4, line 26).

- 3.9 Furthermore, document (4) relates to a class of 5-membered heterocyclic compounds having at least one heteroatom, which are useful in the treatment of a number of diseases including presenile and senile dementia (also known as Alzheimer's disease) (see page 3, lines 1 to 5). Said compounds are defined (see 3, line 6 to page 4, line 50) by the following formula I:



(I)

wherein:

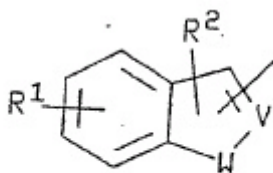
the dotted circle represents one or two double bonds in any position in the 5-membered ring;

X, Y and Z independently represent oxygen, sulphur, nitrogen or carbon;

E represents a bond or a straight or branched and optionally substituted alkylene chain;

F can be a non-aromatic azacyclic or azabicyclic ring system; and

A represents a mandatory group of the following formula II:



(II)

in which W may be, for instance, oxygen or sulphur.

The ring having formula I may be, for instance, furan, but represents in particular a 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole or 1,3,4-thiadiazole ring (see page 3, line 51 to page 4, line 2).

The non-aromatic azacyclic or azabicyclic ring system F in formula I may be, for instance, a quinuclidinenyl group (see the first formula on page 5), but in view of the more detailed technical teaching indicating that a saturated quinuclidinyl or isoquinuclidinyl group belonged to the particularly suitable ring systems (see page 5, line 45 to page 6, line 38, in particular page 5, line 46 and page 6, line 32), the skilled reader of document (4) would rather consider said quinuclidinenyl group as a definitely less preferred one.

The substituent A in formula I having formula II represents in particular an indolyl, benzofuryl or benzothienyl group, and more preferably an indolyl group (see page 4, lines 3 to 30).

Thus starting from the closest prior art, and in particular from the compound of Example 4 mentioned therein (see point 3.3 above), the Board finds that this document (4) does not give the skilled person any pointer to the provision of compounds as now claimed, since not only would he have to disregard its technical teaching about those embodiments of the ring having formula I and the non-aromatic azacyclic or azabicyclic ring system F to be suitably selected, but to delete in addition the mandatory substituent A having formula II or to replace it by R⁴ and/or R⁵ as defined in present Claim 1.

3.10 Finally, the Board finds that document (5) does not give the skilled person an incentive to provide compounds of the application in suit either, since this document only relates to 3-(3-indolyl)-quinuclidine or quinuclidinene derivatives comprising therefore said indolyl substituent as a mandatory feature. Moreover, this document is completely silent about the desired pharmacological activity involving the ability to block or stimulate muscarinic acetylcholine receptors.

3.11 Therefore, documents (3), (4) and (5), taken alone or in combination, do not provide an incentive to the skilled person to arrive at the claimed solution of the above defined technical problem underlying the application in suit.

3.12 In conclusion, the Board finds that the subject-matter of present Claim 1 involves an inventive step in the sense of Article 56 EPC.

4. *Auxiliary requests*

4.1 Having regard to the Board's findings concerning the main request it is not necessary anymore to deal with the more restricted claims of the submitted auxiliary requests.

5. *Remittal to the first instance*

5.1 The decision under appeal only concerned the patentability of Claim 1 then on file. Therefore, the application in suit as a whole needs further examination in order to establish whether it meets the requirements of the EPC. In these circumstances, and in accordance with the Appellant's request, the Board finds it appropriate to make use of its power under Article 111(1) EPC and to remit the case to the first instance for further prosecution.

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 claims of the main request filed on 24 January 2000.

The Registrar:

The Chairman:

N. Maslin

A. Nuss