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D E C I S I O N
of 14 October 1996

Case Number: T 0643/96 - 3.3.1

Application Number: 88312038.8

Publication Number: 0322182

IPC: C07D 453/02

Language of the proceedings: EN

Title of invention:
Azabicyclic compounds, process for their preparation and pharmaceutical compositions containing them

Applicant:
BEECHAM GROUP PLC

Opponent:
-

Headword:
Bioisosterism/BEECHAM

Relevant legal provisions:
EPC Art. 52(1), 56, 113(1)

Keyword:
"Inventive step (yes) - no pointer to claimed compounds"

Decisions cited:
T 0852/91, T 0548/91, T 0309/91

Catchword:
1. The concept of bioisosterism has to be applied with caution when deciding upon inventive step (No. 4.2.3.3).

2. When deciding upon inventive step in relation to pharmacologically active compounds, what is essential is not whether a particular substructure of a chemical compound is replaced by another known isosteric one, but whether information was available on the impact of such a replacement on the pharmacological activity profile of the specific (group of) compound(s) concerned (No. 4.2.3.5).

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0643/96 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 14 October 1996

Appellant: BEECHAM GROUP PLC
Beecham House
Great West Road
Brentford
Middlesex TW8 9BD (GB)

Representative: Russell, Brian John
SmithKline Beecham plc
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 1 March 1996 refusing European patent application No. 88 312 038.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

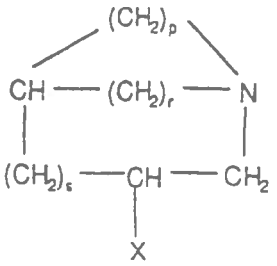
Chairman: A. J. Nuss
Members: P. Krasa
R. E. Teschemacher

Summary of Facts and Submissions

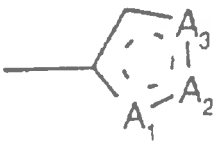
I. This appeal lies from the decision of the Examining Division refusing European patent application No. 88 312 038.8 (publication No. 0 322 182), filed on 19 December 1988 and claiming three priorities from the United Kingdom as of 22 December 1987, 27 May 1988, and 13 October 1988.

Independent Claim 1 for all the designated contracting states other than ES, as amended by the Appellant with his letter of 3 August 1995, reads as follows:

"1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



in which p represents an integer of 2 to 4; r represents an integer of 1 or 2; s represents 0 or 1; and X represents a group



in which A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_1 and the other is nitrogen or CR_2, or A_2 is oxygen or sulphur, A_1 is CH and A_3 is CR_1, where R_1 and R_2 are independently selected from hydrogen and C_{1-2} alkyl, with the proviso that when r is 2, R_1 and R_2 are independently hydrogen or methyl, provided also that when A_1 is oxygen or sulphur and A_3 is nitrogen, (p,r,s) is other than (2,2,0) or (2,1,0)."

II. The Examining Division, applying the concept of "bioisosterism", refused the application on the grounds that the subject-matter of Claim 1 was not inventive over documents

(1) EP-A-0 239 309,
(2) DE-A-1 938 546, and
(3) C.W. Thornber "Isosterism and Molecular Modification in Drug Design", Chem. Soc. Reviews 18 (1979), 563-580.

Document (3) had been introduced by the Appellant into the examination proceedings by his letter dated 3 August 1995 as supporting evidence for his argument that the subject-matter of the application in suit was not obvious according to the said concept of "bioisosterism".

Further, the Examining Division relied on a document

(5) designated as "Pharmaceutical Sciences, 1985, chapter 27, page 446, Table II".

This document was cited for the first time in the decision under appeal. A copy of the document was not sent to the Appellant as can be seen from page 2 of the decision under appeal where it is not mentioned under "Enclosures".

The Board will also refer to

(4) EP-A-0 261 763

published on 30 March 1988 (i.e. in the interval between the first and second priority dates claimed for the present application) and cited in the application in suit (page 3, line 4).

III. The Appellant, in his Statements of Grounds of Appeal, submitted in essence that document (2) disclosed muscarinic antagonists with anti-cholinergic activity which were to be used in the treatment of Parkinson's disease as an anti-histamine, a neurosedative or as a tranquilliser, and not as an anti-dementia agent like the compounds of present Claim 1. He concluded that document (1) was, therefore, of no relevance in respect of inventive step.

Further, the Appellant submitted that citation (1) gave no indication which of the many structural features of the disclosed compounds with (partial) muscarinic agonist activity could be varied with a reasonable expectation of retaining the desired activity. Referring to document (3) in support, the Appellant submitted that such a reasonable expectation of success could not be based on the concept of bioisosterism.

Finally, the Appellant submitted that the reference to citation (5) was unclear and that he had been unable to locate it.

IV. Responding to a telephone message from the Rapporteur, indicating that the claims submitted by the letter dated 3 August 1995 seemed to be incomplete (not in respect of Claim 1 for all the designated states other than Spain), the Appellant submitted on 13 September 1996 a complete set of Claims 1 to 11 for all designated states except Spain and of Claims 1 to 8 for Spain and requested that the decision under appeal be set aside and a patent be granted on the application in suit on the basis of those claims.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

Present claims 1 to 11 for all the designated contracting states except ES and present claims 1 to 8 for ES clearly comply with the requirements of Article 123(2) EPC. Since this is not in dispute, no further comments from the Board are required.

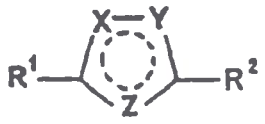
3. *Novelty*

The subject-matter of the claims is not disclosed in any of the citations on file and is, therefore, novel. Since this is not in dispute, no further comments from the Board are necessary on this issue either.

4. *Inventive Step*

4.1 The Examining Division considered document (1) to represent the most relevant state of the art. The Board has no reason to disagree and accepts this citation as the starting point for the evaluation of inventive step.

Document (1) discloses that oxadiazoles of the general formula



or salts thereof, wherein

one of X, Y, or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus;

R^1 represents a non-aromatic azacyclic or azabicyclic ring system; and

R^2 is a substituent of low lipophilicity,

are useful in the treatment of, *inter alia*, presenile and senile dementia (page 3, lines 1 to 21, in combination with page 1, lines 1 to 12).

It follows that the technical problem to be solved can be seen in providing further chemical compounds useful in the treatment and/or prophylaxis of dementia in mammals.

In view of the reported radio ligand binding tests which are indicative for the muscarinic binding activity of the tested compounds (page 30, line 49 to page 31, line 35 and page 31, line 7 of the application in suit as published) which in turn is indicative of their usefulness as anti-dementia agents (page 3, lines 8 to 10 of the application in suit as published), the Board is satisfied that the subject-matter of Claim 1 solves the said technical problem.

4.2 It remains to be decided whether or not the compounds of Claim 1 of the application in suit meet the requirement of inventive step.

4.2.1 The group of compounds generically disclosed in document (1) are either 1,2,4-oxadiazoles or 1,3,4-oxadiazoles, both necessarily substituted with a non-aromatic azacyclic or azabicyclic ring system comprising an unlimited number of ring atoms with the nitrogen atom in any conceivable position. 1-aza-[2,2,2]-bicycloctyl (quinuclidinyl) and 1-aza-[2,2,1]-bicycloheptyl (1-azanorbornyl) are identified, *inter alia*, as possible aza-ring systems and further supported in the examples (page 4, formulae, and e.g. examples 10, 11, 15, 24, 34).

The compounds of present Claim 1 differ from those of document (1) mainly in the replacement of the five-membered, aromatic oxadiazole system comprising three hetero-atoms by a five-membered, aromatic system comprising only one or two hetero-atoms, i.e. furan, thiophene, 1,2-oxazole, 1,3-oxazole, 1,2-thiazole, or 1,3-thiazole (see point I above).

4.2.2 Referring to the compounds of document (1), the Examining Division stated

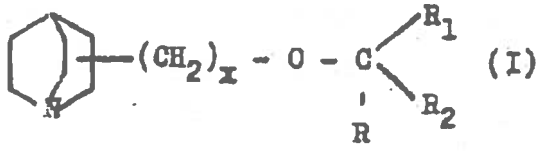
"From the formula of these compounds it could be taken that the essential part was the azabicyclic ground structure with the heterocyclic substituent as the necessary complementary part, all the more so since D2 discloses compound having a related usefulness (cf. page 12, third paragraph or Table III on page 35) with such a bicyclic moiety. The person skilled in the art having to solve the above problem could further conclude and expect that the replacement of the oxadiazole group by other heterocyclic substituents known to be **possible bioisosters** could solve the problem"

(page 4, first paragraph of the decision under appeal; emphasis added). Relying on document (3), the Examining Division further argued that "-CH=CH-, -O-, -S- and =N-" (-CH=CH- is obviously a misprint for -C=) were known as possible ring equivalents and it was therefore obvious for the skilled person to try structural modifications on the basis of the interchangeability of those sub-structures when looking for alternatives to the compounds known from document (1).

4.2.3 This line of argument is not convincing for the following reasons.

4.2.3.1 First of all, the Board notes that document (1) leaves room for broad variations in respect to the non-aromatic azacyclic or azabicyclic ring system, whereas the oxadiazole system is disclosed as a mandatory structural feature of the respective compounds. Thus, in the Board's judgement, and contrary to the Examining Division's interpretation, document (1) discloses that the two particular five-membered, aromatic oxadiazole heterocycles are the essential sub-structures, whereas the nature of the non-aromatic azacyclic or -bicyclic residue is not so crucial.

4.2.3.2 Document (2), relied on by the Examining Division, discloses compounds of the following formula



(I)

The definitions of R, R_1, R_2, and x are of no relevance to the present case; it is sufficient to note that these compounds do not contain a five-membered, aromatic, heterocyclic moiety linked to the azabicyclic sub-structure. The compounds of document (2) are useful as anti-histamines, neurosedatives, tranquillisers, and for the treatment of Parkinson's Disease (page 12, lines 9 to 12, in combination with page 1). Thus, their field of application, designated by the Examining Division too as only "related usefulness", differs from that of the compounds of the present application, namely treatment and prophylaxis of dementia. The Examining Division gave no arguments why a skilled person would have ignored such a difference when looking for a solution to the existing technical problem. The Board, accepting the Appellant's argument that document (2) is not relevant in the present context, therefore concludes that this

citation does not confirm the Examining Division's allegation that the two particular five-membered, aromatic oxadiazole heterocyclic residues are not essential features of the compounds disclosed in document (1).

4.2.3.3 The above quoted argument of the Examining Division (see No. 4.2.2) amounts in fact to an allegation that the existing structural differences between the compounds known from document (1) and those now claimed are so small that a skilled person would have known that such differences have no essential bearing on the properties important for solving the technical problem (T 0852/91, No. 8.2 of the Reasons for the Decision, not published in the OJ EPO). The validity of this argument hinges on the applicability of the concept of bioisosterism from which the skilled person would have drawn this knowledge.

The Board agrees that this concept belongs to the common general knowledge of those skilled in the art but, in the Board's judgement, it has to be applied with caution when deciding upon inventive step. In the field of drug design any structural modification of a pharmacologically active compound is, in the absence of an **established** correlation between structural features and activity, *a priori* expected to disturb the pharmacological activity profile of the initial structure. This holds true also for an alleged case of bioisosterism, which is one option of a structure-activity relationship, as long as it is not an **established** case of bioisosterism (see also T 0548/91, No. 6.4 of the Reasons for the Decision, not published in the OJ EPO).

A careful evaluation of all relevant circumstances is therefore required as to whether or not that *a priori* assumption can indeed be overcome with the aid of the concept of bioisosterism (which in essence is not a law of nature of general validity but rather an **empirical rule**, which in each particular case needs to be experimentally verified in order to establish whether or not it fits).

In document (3) the concept of bioisosterism is discussed. It is explained that in any bioisosteric replacement a considerable number of different, independent parameters could be considered: "The extent to which the replacement is useful will depend upon which of these parameters is important and which ones the bioisostere can best mimic ... Usually one will not know which role(s) the various parts of the molecule play(s) in its action and this determination will be part of the structure-activity study". The document concludes, *inter alia*, that "Whether the same or a different biological activity results from the replacement will be governed by the role(s) which that moiety fulfils in the molecule and whether parameters affecting that role have been disturbed" (page 565, lines 16 to 19, and the last three lines; page 566, lines 3 to 5).

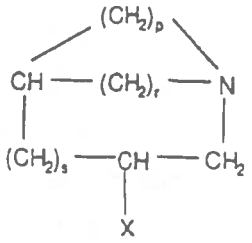
This clearly confirms that the concept of bioisosterism - at least in the circumstances of this case - is to be considered at most as providing some general guidance to the skilled person developing a research program in the particular pharmacological field, but certainly not as a pointer to the solution to the existing technical problem as now claimed (see also T 0309/91, No. 4.2.4 of the Reasons for the Decision, not published in the OJ EPO).

4.2.3.4 The Examining Division further relied on document (5) in support of the statement that the bioisosteric groups concerned (see above No. 4.2.2) were generally known as isosters. Only incomplete bibliographic data of this citation were given in the decision under appeal and no copy was provided to the Appellant who requested one in his Grounds for Appeal. The Board identified this citation as "*Remington's* Pharmaceutical Sciences, 1985, chapter 27, page 446, Table II". The table lists more or less the same groups as the isosteric ones already listed in document (3) and therefore adds nothing to the present case. For this reason, the Examining Division's failure not to provide the Appellant with a copy of document (5) does not amount to a substantial procedural violation and the Board could decide this case without providing the Appellant (who never denied that the groups concerned were known as isosters) with such a copy and without thereby violating the Appellant's right to be heard (Article 113(1) EPC).

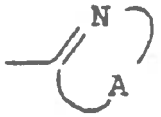
4.2.3.5 However, when deciding on inventive step in relation to pharmacologically active compounds, what is essential is not whether a particular sub-structure of a chemical compound is replaced by another known isosteric one, but whether information was available on the impact of such a replacement on the pharmacological activity profile of the (group of) specific compound(s) concerned. The Examining Division did not refer to, nor is the Board aware of, such information.

4.2.3.6 The Board has, of its own motion, also considered document (4), of which the Appellant is the author. This document is state of the art only for such claimed subject-matter as is not entitled to the first priority date claimed for the application in suit. Document (4) discloses compounds of the following

formula



in which X represents a group



wherein.... A represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, ... (only the definition important for the present case has been given)

as useful anti-dementia agents (page 3, lines 5 to 35).

A mandatory structural feature of these compounds is a =N- atom adjacent to the C-atom linking the five-membered, aromatic heterocyclic residue to the non-aromatic azabicyclic moiety. The same mandatory structural feature is to be found in the compounds disclosed in document (1); see No. 4.2, above. Thus, in the Board's judgement, a skilled person would have assumed that this structural feature is a necessary requirement for maintaining the desired properties of the compounds concerned. In the absence of further information, he would not have expected that a replacement of this =N-atom by the isosters -O-, -S-, or =CH- (as in the compounds of present Claim 1) would result in compounds retaining the desired anti-

dementia activity.

4.3 It follows from the above that the subject-matter of Claim 1 for the designated contracting states except Spain is not rendered obvious by documents (1) to (5), either alone or in combination. Dependent Claims 2 to 6 relating to specific embodiments of this invention, Claim 7 relating to a process for the preparation of the compounds of Claim 1, Claim 8 relating to pharmaceutical compositions comprising them, Claims 9 and 10 directed to a compound of Claim 1 for use as a therapeutical substance, and Claim 11 directed to the use of a compound of Claim 1 in the preparation of a medicament are based on the same inventive concept and derive their patentability from that of Claim 1, as do Claims 1 to 8 for Spain.

Order

for these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant a patent on the basis of the following documents:

   - Claims 1 to 11 for all the designated contracting states except Spain, as filed by fax on 13 September 1996;

   - Claims 1 to 8 for Spain, as filed by fax on 13 September 1996;

   - a description to be adapted accordingly.

The Registrar:

E. Görgmaier

The Chairman:

A. Nuss