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D E C I S I O N
of 21 August 1997

Case Number: T 0795/94 - 3.3.1

Application Number: 89303653.3

Publication Number: 0339834

IPC: C07D 471/08

Language of the proceedings: EN

Title of invention:

Heterocyclic compounds, process for their preparation and pharmaceutical compositions containing them,

Applicant:

Beecham Group plc

Opponent:

-

Headword:

Azabicyclic compounds/BEECHAM

Relevant legal provisions:

EPC Art. 56

Keyword:

"Biological activity of bridgehead substituted compounds not suggested"

"Credibility of alleged effect"

"Inventive step - yes, after amendment"

Decisions cited:

-

Catchword:

-



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Boards of Appeal

Chambres de recours

Case Number: T 0795/94 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 21 August 1997

Appellant: Beecham Group plc
Beecham House
Great West Road
Brentford
Middlesex TW8 9BD (GB)

Representative: Tocher, Pauline
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 29 April 1994
refusing European patent application
No. 89 303 653.3 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: R. K. Spangenberg
Members: P. Bracke
A. C. G. Lindqvist

Summary of Facts and Submissions

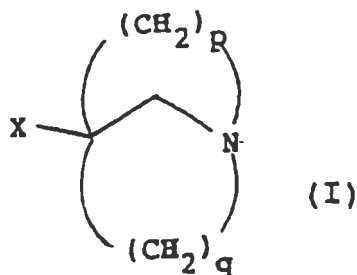
- I. The appeal lies from the Examining Division's decision, dispatched on 29 April 1994, refusing European patent application No. 89 303 653.3, published as EP-A-0 339 834. The decision under appeal was based on two sets of claims, one for all Contracting States other than Spain, comprising Claims 1 to 4 and 6 to 11 as originally filed and Claim 5 filed with the letter dated 16 February 1994, and the other, comprising Claims 1 to 8 as originally filed for the Contracting State Spain.

- II. The Examining Division considered that, since it was known from document (2) (EP-A-0 239 309) that oxadiazoles attached to an azabicyclic ring system are potent muscarinic agonists, irrespective of the bonding site of the oxadiazole to the azabicyclic moiety, it could be expected that compounds having the oxadiazolyl group attached to the bridgehead of an azabicyclic system would also be potent muscarinic agonists, so that the claimed subject-matter lacked inventive step.

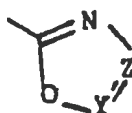
- III. In reply to observations of the Board of Appeal the Appellant filed two amended sets of claims for all Contracting States, denoted as "SET 1", comprising 11 claims, and one comprising 9 claims, denoted as "SET 2", with a letter dated 11 April 1997.

Claim 1 of SET 1 read:

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



in which X represents a group



wherein one of Y and Z represents nitrogen and the other represents CR where R is selected from halogen, CN, OR^1 , SR^1 , $N(R^1)_2$, NHR^1 , $NHCOR^1$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR^1$, $NHNH_2$, COR^1 , COR^2 , C_{2-4} alkenyl, C_{2-4} alkynyl or C_{1-2} alkyl substituted with OR^1 , $N(R^1)_2$, SR^1 , CO_2R^1 , $CON(R^1)_2$ or one or two halogen atoms, in which R^1 is hydrogen or C_{1-2} alkyl and R^2 is OR^1 , NH_2 or NHR^1 ; and each of p and q independently represents 2 or 3." (emphasis added)

Claims 2 to 5 were dependent on Claim 1; Claims 6 and 7 related to a process for preparing compounds of formula (I); whereas Claim 8 concerned a pharmaceutical composition comprising a compound of formula (I), Claim 9 and 10 a compound of formula (I) for use as an

active therapeutic substance or for use in the treatment and/or prophylaxis of dementia, respectively and Claim 11 the use of a compound of formula (I) in the preparation of a medicament for the treatment and/or prophylaxis of dementia.

IV. The Appellant submitted that a skilled person would not construe the disclosure of document (2) so as to embrace the possibility of bridgehead substitution and argued that the claimed compounds were inventive, because document (2) and the prior art as a whole suggested neither preparing the presently claimed bridgehead substituted azabicyclic compounds nor that compounds having such rigid structures would have agonistic properties at muscarinic receptors.

V. In support of his allegation that the complete scope of the claimed compounds have agonistic properties at muscarinic receptors, the Appellant supplied, during the oral proceedings held on 21 August 1997, a sheet having the title "Data comparison", with the IC_{50} -values (the concentration which inhibits binding of the ligand by 50%) for the displacement of the muscarinic agonist 3H-OXO-M [$IC_{50}(3H-OXO-M)$] and the ratio of the IC_{50} -values for the displacement of the muscarinic antagonist 3H-QNB [$IC_{50}(3H-QNB)$] to $IC_{50}(3H-OXO-M)$ for the compounds E9, E10, E11, E13, E14 and E17 described in document (1) (EP-A-0 287 356) and the compounds E1, E2, E4 and E5 according to the application in suit.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of:

the main request: Claims 1 to 11 according to "SET 1" for all contracting states, filed with letter of 11 April 1997,

the **auxiliary request**: Claims 1 to 9 according to "SET 2" for all contracting states, filed with letter of 11 April 1997.

Reasons for the Decision

1. The appeal is admissible.
2. *Main request*
- 2.1 Amendments

The wording of Claim 1 essentially differs from that of Claim 1 as filed by the feature described in the emphasised part of present Claim 1 (see point III above), which feature was disclosed on page 2, lines 29 and 30, of the application as filed (page 3, line 42, of the published version). Claims 2 to 11 correspond with the originally filed Claims 2 to 11, except that the last two compounds listed in Claim 5 as originally filed, which were not entitled to the claimed priority date, are deleted, and that the wording of Claim 6 was amended to correspond to the amended Claim 1. The requirement of Article 123(2) EPC is therefore met.

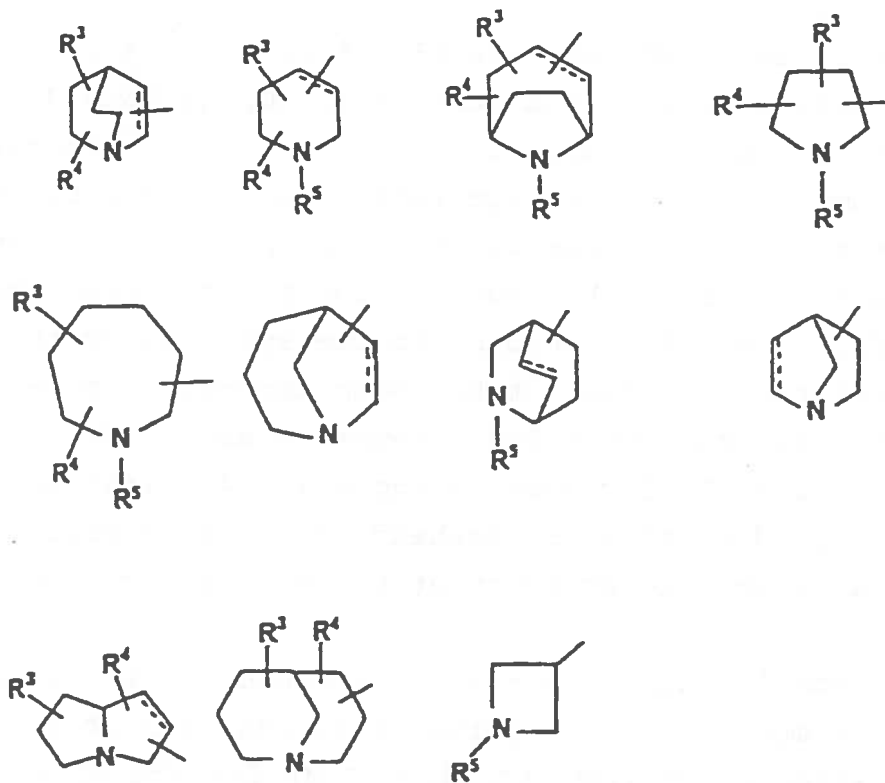
- 2.2 Novelty

Since azabicyclic ring systems having an oxadiazole ring substituted on its bridgehead are not described in document (2) and since the claimed compounds differ from those described in document (1) at least by the

nature of the substituent R in the oxadiazole ring, the Board is satisfied that the claimed subject-matter is novel over the only two documents cited in the European search report.

2.3 Inventive step

2.3.1 Document (2), the only document cited as state of the art according to Article 54(2) EPC and mentioned on page 3, lines 3 and 4, of the application in suit, is concerned with oxadiazoles, substituted with *inter alia* a non-aromatic azabicyclic ring system, which are potent muscarinic agonists (page 2, lines 14 to 26). The oxadiazoles may be 1,3,4- or 1,2,4-oxadiazoles (page 3, lines 17 and 18) and the non-aromatic azabicyclic ring system may be one according to the following formulas



including azabicyclo[2.2.1]heptanes, azabicyclo[3.2.1]octanes and azabicyclo[3.3.1]nonanes (see the sixth, eighth and tenth of the above structures).

- 2.3.2 Starting from the teaching of document (2), the problem underlying the invention was the provision of further compounds which enhance acetylcholine function via an action at muscarinic receptors within the central nervous system and are therefore of potential use in the treatment and/or prophylaxis of dementia in mammals (page 3, lines 3 to 7, of the application in suit).
- 2.3.3 In assessing inventive step, the first point to be considered is whether it has been convincingly shown that the claimed compounds effectively do have such activity.

Since it is taught on page 13, lines 47 to 49, of the application in suit that the ratio $IC_{50}(3H-QNB)/IC_{50}(3H-OXO-M)$ gives an indication of the agonist character of the compounds and that agonists typically exhibit a large ratio, and since it has been shown in the report "Data comparison" that such ratios for the compounds E1, E2, E4 and E5 according to the application in suit are relatively large, it has been demonstrated beyond doubt that azabicyclo[2.2.1]heptanes and azabicyclo[3.2.1]octanes having a 1,2,4-oxadiazol-5-yl substituted on their bridgehead carbon atom effectively have an agonistic activity at the muscarinic receptor.

Additionally, with the ratios provided in the report "Data comparison" (see point V) it has been shown that the ratio $IC_{50}(3H-QNB)/IC_{50}(3H-OXO-M)$ for the claimed compounds is of a similar size to the ratio for compounds described in document (1), a prior patent

application by the Appellant which belongs to the state of the art according to Article 54(3) EPC, namely azabicyclo[2.2.1]heptanes, azabicyclo[3.2.1]octanes and azabicyclo[3.3.1]nonanes having a 1,2,4-oxadiazol-5-yl group substituted on the bridgehead carbon atom (E9, E10 and E11) and azabicyclo[2.2.1]heptanes and azabicyclo[3.2.1]octanes having a 1,3,4-oxadiazol-5-yl group substituted on the bridgehead carbon atom (E13, E14 and E17).

Therefore, the Board accepts that it has been convincingly shown that the azabicyclo[3.3.1]nonanes having an oxadiazole substituted on their bridgehead carbon atoms, as defined in present Claim 1, also have agonistic properties at the muscarinic receptors.

Moreover, since document (2), page 2, line 14 to page 3, line 21, shows that the 1,3,4-oxadiazole- as well as 1,3,4-oxadiazole substituted azabicyclic compounds described therein are potent muscarinic agonists, in the absence of any indication to the contrary, the Board accepts that an 1,3,4-oxadiazole nucleus and an 1,2,4-oxadiazole nucleus have equivalent muscarinic agonistic activity as substituents on azabicyclic compounds.

Consequently, in the Board's view it can be assumed, on the balance of probabilities, that all compounds resulting from any claimed combination of an oxadiazole and an azabicyclic ring would have similar muscarinic agonistic activity.

2.3.4 It remains to be decided whether it could have been derived from the teaching of document (2) that the claimed azabicyclic compounds having an oxadiazole substituted on the bridgehead carbon atom would have these properties.

Since it was known from document (2) that the above-mentioned azabicyclic systems may be a monocycle as well as a fused, spiro or bridged bicycle (page 3, lines 28 and 29) and, according to the formulas given on page 4 of document (2), the oxadiazolyl group can be attached to any ring member of the azabicyclic ring system, the Examining Division concluded that, according to the teaching of document (2), the azabicyclic ring system may be varied to a considerable extent while the qualitative activity of the resulting compounds is expected to be retained.

- 2.3.5 However, in assessing inventive step in the present case it is not relevant whether it could be derived from document (2) that the azabicyclic system may be varied to a considerable extent, since the only relevant question is whether it could be derived therefrom that azabicyclic ring systems having an oxadiazole nucleus substituted on a **bridgehead carbon atom** thereof would have the mentioned activity.

Since such bridgehead-substituted azabicyclic ring systems were not specifically described in document (2), which has never been contested, the answer to this question hinges on the interpretation of the disclosure of document (2) and, in particular, on the answer to the question whether by the undefined stroke in the bicyclic structures at the top of page 4 of document (2) (see point 2.3.1 above) the bridgehead-substituted compounds would also have been contemplated.

- 2.3.6 In the Board's judgment this is not the case. The Board agrees with the Appellant's submission that, in the absence of any disclosure of the necessary starting compounds for obtaining bridgehead-substituted compounds, document (2) does not contain an enabling

disclosure relating to those compounds. In addition, the Board considers that, as a rule, a skilled person would consider general disclosures, like the ones on page 4 of document (2), as relating solely to the substitution on **structurally equivalent** carbon atoms.

However, the methods of preparing the compounds described in document (2) are only related to oxadiazole-forming cyclisation reactions of intermediates already containing the azabicyclic ring (see page 10, line 1, to page 15, line 28), which are totally different from the methods disclosed in the patent in suit. Furthermore, azabicyclo[2.2.1]heptanes and azabicyclo[3.2.1]octanes are only described in examples 19, 24 and 27 of document (2) and in none of them does the oxadiazole ring substitute the hydrogen atom on a bridgehead carbon atom. Therefore, the Board holds that document (2) does not contemplate bridgehead substitution and, therefore, cannot suggest any biological activity of such bridgehead-substituted compounds.

- 2.3.7 On the basis of this construction of the disclosure of document (2), and considering that the Board is not aware of any evidence contradicting the Appellant's argument that by substituting the bridgehead carbon atom of an azabicyclic ring system according to the present Claim 1 the configuration of the ring system is locked, and that it could not have been predicted *a priori* that such a rigid structure would still meet the strict requirements of structurally fitting (spatially and electronically) with an acetylcholine receptor in order to have agonistic properties at the muscarinic

receptor, the Board concludes that a skilled person would not have derived from the available prior art that the claimed bridgehead-substituted azabicyclic compounds would have agonistic properties at muscarinic receptors.

2.3.8 Claims 2 to 5, which represent preferred embodiments of Claim 1, the process Claims 6 and 7, the composition Claim 8, the compound Claims 9 and 10 and the use Claim 11 derive their patentability from that of Claim 1.

2.4 Since Claims 1 to 11 according to the main request comply with the requirements of the EPC, a European patent may be granted on the basis of this set of claims.

3. *Auxiliary request*


In the light of the above findings, there is no need to consider the auxiliary request.

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 Claims 1 to 11 submitted as "SET 1" (main request) on 11 April 1997 and a description to be adapted as necessary.

The Registrar:


E. Görgmäyer

The Chairman:


R. Spangenberg

