BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

A		B		C	X

File Number: T 309/91 - 3.3.1

Application No.: 84 105 158.4

Publication No.: 0 126 367

Title of invention: Active compounds

Classification: C07D 311/08

D E C I S I O N
of 28 January 1993

Applicant: Beecham Group PLC

Proprietor of the patent:

Opponent:

Headword: Benzopyrans/BEECHAM

EPC Article 56

Keyword: "Inventive step (confirmed)"

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 309/91 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 28 January 1993

Appellant : Beecham Group PLC
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Decision under appeal : Decision of the Examining Division 007 of the European Patent Office dated 7 December 1990 refusing European patent application No. 84 105 158.4 pursuant to Article 97(1) EPC.

Composition of the Board :

Chairman : K.J.A. Jahn
Members : R.W. Andrews
J.-C. Saisset

Summary of facts and submissions

I. European patent application No. 84 105 158.4 (publication No. 0 126 367) was filed on 7 May 1984 claiming priority from four prior applications filed on 18 May 1983 in the United Kingdom.

II. By a decision dated 7 December 1990, the Examining Division refused the application on the ground that the subject-matter of the Claims 1 to 10 filed on 9 June 1989 did not involve an inventive step in the light of the disclosure in various documents, including, inter alia:

(1) EP-A- 0 095 316

(2) EP-A- 0 076 075

(4) EP-A- 0 028 064

(5) EP-A- 0 046 652

(6) US-A- 4 110 347

(7) Chemical Society Reviews, Volume 18, pages 563 to 580 (1979)

(8) Design of Biopharmaceutical Properties through Prodrugs and Analogs, American Pharmaceutical Association Academy of Pharmaceutical Sciences, pages 230 to 235 (1977) and

(10) EP-A- 0 093 535

The Examining Division considered that the solution to the problem of providing novel antihypertensive benzopyrans having a new type of substituent in the 4-position was

obvious since the skilled person applying the prodrug approach disclosed in document (8) and, in view of the list of reversible groups given in Table II thereof, would replace the 4-NR^1R^2 of the compounds of, for example, document (6) by the present 4-substituents.

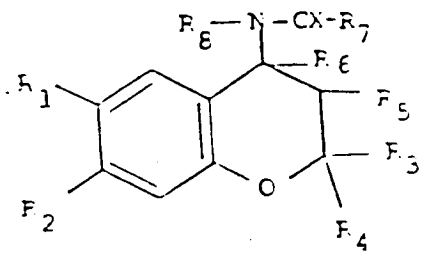
III. An appeal was lodged against the decision on 26 January 1991 with payment of the prescribed fee. In his statement of grounds of appeal filed on 5 April 1991 and in his reply to the Rapporteur's letter of 14 April 1992 filed on 14 December 1992, the Appellant denied that document (8) provided any general incentive to prepare either the compounds entitled to the priority date of 18 May 1983 or those entitled to the filing date of 7 May 1984. The Appellant argued that ureides and carbamates are functionally different substituents as compared with either amines or cyclic amides and that it is known that differences in functionality can produce marked qualitative differences in pharmacological properties. In the absence of any knowledge of the putative receptor and receptor interaction, and the effects on drug activity of basicity, steric and other numerous factors, the skilled person could not predict that the present compounds would show any antihypertensive activity.

In the Appellant's opinion, the concept of isosteric replacement is a very simplistic one and takes little account of the profound changes in physical, biochemical and biological properties that can result from even small structural changes in a molecule. Furthermore, the skilled person is aware that electron distribution within the molecule is as important in receptor binding as steric factors. In any case, since the conformations required for the activity of the prior art compounds are not known, it would be impossible for the skilled person to predict

whether the present compound would adopt similar conformation and, therefore, possess antihypertensive activity.

IV. The Appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 to 10 filed on 9 June 1989. Claim 1 of this set of claims reads as follows:

"A compound of formula (I):



(I)

wherein:

either one of R_1 and R_2 is hydrogen and the other is selected from the class of C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylhydroxymethyl, nitro, cyano, chloro, trifluoromethyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, C_{1-6} alkyl-thiolmethyl, formyl or aminosulphinyl, aminosulphonyl or aminocarbonyl, the amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino, C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino or ethlenyl terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or one of R_1 and R_2 is nitro, cyano or C_{1-3}

alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl groups or by C_{2-7} alkanoyl;

one of R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene;

either R_5 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_6 is hydrogen or R_5 and R_6 together are a bond;

R_7 is amino optionally substituted by a C_{1-6} alkyl group or by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or C_{1-6} alkoxy, or phenoxy optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

R_8 is hydrogen or C_{1-6} alkyl; and

X is oxygen or sulphur;

the R_8-N-CX-R_7 group being trans to the R_5 group when R_5 and R_6 together are not a bond;

or, when the compound of formula (I) contains a salifiable group, a pharmaceutically acceptable salt thereof."

Claims 2 to 5 relate to preferred compounds according to Claim 1. Claim 6 concerns a process for the manufacture of compounds of Claims 1 to 5. Claim 7 relates to a pharmaceutical composition comprising a compound of Claims 1 to 5. Claims 8 and 9 claim a compound according to Claims 1 to 5 for use as an active therapeutic substance and in the treatment or prophylaxis of

hypertension in mammals respectively. Claim 10 relates to the use of a compound of Claims 1 to 5 in the manufacture of a medicament in the treatment of hypertension in mammals.

Reasons for the decision

1. The appeal is admissible.

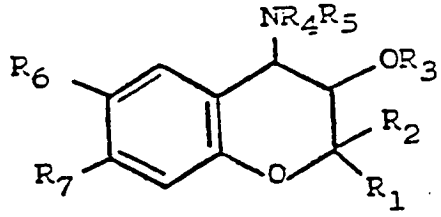
2. There are no objections under Article 123(2) EPC to the present version of the claims. In particular, Claims 1, 3, 4, 6 and 7 are based on original Claims 1, 6, 7, 8 and 9 respectively. Claim 2 finds a basis on page 4, lines 28 to 35. The compound claimed in Claim 5 (after the correction of a clerical error by the insertion of "6-" between "trans-" and "Cyano") is disclosed in Example 3. Claims 8 to 10 find a basis on page 1, lines 9 and 10 and page 21, lines 1 to 25.

3. After examination of the cited prior art, the Board has reached the conclusion that the claimed subject-matter is novel. Since in the decision under appeal the Examining Division acknowledged the novelty of the subject-matter of the present claims, it is not necessary to give detailed reasons for this finding.

4. It still remains to be decided whether the claimed subject-matter involves an inventive step.

4.1 Subject-matter entitled to the priority date 18 May 1983; i.e. compounds of the formula I wherein R_1, R_2, R_3, R_4, R_7, R_8 and X are as defined in the present Claim 1 and either R_5 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_6 is hydrogen or R_5 and R_6 together are a bond.

4.1.1 In the Board's judgement, the closest prior art to this subject-matter is document (4) which discloses benzopyran-3-ols of the formula I



(I)

and salts thereof, wherein R_1, R_2, R_3 and R_4 each are a hydrogen atom or a lower alkyl group, R_5 is an optionally substituted alkyl group, R_4 and R_5 are joined so that together with the nitrogen atom to which they are attached they form a 5-, 6- or 7-membered ring optionally containing an oxygen or sulphur atom, R_6 is an electron donoting group such as amino, lower acylamino, lower alkylamino, lower dialkylamino, hydroxy, lower alkoxy and lower alkyl; R_7 is an electron withdrawing group such as nitro, cyano, carboxamido, acetyl and lower alkoxycarbonyl, and the group NR_4R_5 is trans to the OR_3 group (cf. Claim 1 in combination with page 3, lines 4 to 6). These prior art compounds also possess antihypertensive activity (cf. Claim 11 and Example 3).

In the light of this closest state of the art, the technical problem underlying the application with respect to this subject-matter is to be seen in providing further benzopyrans having antihypertensive activity. According to the application this problem is essentially solved by replacing optionally substituted amino group $-NR_1R_2$ at the 4-position of the known benzopyrans by an optionally substituted ureido or thioureido group, an alkoxycarbonylamino group, an alkoxythiocarbonylamino group, an optionally substituted phenoxycarbonylamino group or an optionally substituted phenoxythiocarbonyl-amino group.

In view of the pharmacological data on pages 32 to 34 of the disputed patent application and the evidence in the Journal of Medicinal Chemistry, Volume 33, No. 9, pages 2667 to 2672, 1990, in particular compounds 31 to 36 and 39 in Table IV, the Board is satisfied that this technical problem has been solved.

4.1.2 As previously mentioned, document (4) discloses benzopyrans with an optionally substituted amino group at the 4-positions having antihypertensive activity. Documents (2), (5) and (6) also describe benzopyrans substituted in the 4-position having antihypertensive activity. In particular, document (2) discloses benzopyrans having either a 2-oxopiperidino or 2-oxo-1-pyrrolidinyl radical at the 4-position (cf. Claim 1); document (5) describes benzopyran derivatives having a haloalkylamino radical at this position (cf. Claim 1) and document (6) discloses benzopyrans with a group of the formula NR_1R_2 at the 4-position, wherein R_1 is a hydrogen atom or a C_{1-9} hydrocarbyl radical optionally substituted by a hydroxy or C_{1-6} alkoxy radical, R_2 is a hydrogen atom or a C_{1-6} alkyl radical or NR_1R_2 is a 3 to 8 membered heterocyclic group optionally substituted by one or two methyl groups (cf. column 1, lines 18 to 48).

Therefore, documents (2), (4), (5) and (6) teach that benzopyrans having an optionally substituted amino group or a CON- as part of a ring possess antihypertensive activity. However, there is no indication in these documents which would lead the skilled person to expect that the solution to the present technical problem would lie in the provision of compounds in which the substituent at the 4-position is an optionally substituted (thio) ureido group, an alkoxy(thio)carbonylamino group or an optionally substituted phenoxy(thio)carbonylamino group. In other words, changing from compounds which may be classed as amines or lactams to ureas, thioureas, carbamates and thiocarbamates.

Document (8) discloses in very general terms the prodrug approach to the design of pharmaceutical compounds but is silent on the basic structure or even the activity to which this principle can be applied. This document contains a list of reversible functional groups suitable for the preparation of prodrugs. However, in the absence of any indication that the lactams of document (2) are prodrugs which develop their antihypertensive activity by the hydrolysis of the cyclic amide group, document (8) would not provide with any incentive to investigate the possibility of preparing prodrugs for the optionally substituted amines of documents (4), (5) and (6). Although document (4) refers to prodrugs (cf. Claim 1), the only suitable prodrugs mentioned therein are esters of the hydroxy group at the 3-position (cf. page 3, lines 16 to 22).

Therefore, in the Board's judgement, the subject-matter entitled to the priority date 18 May 1983 involves an inventive step.

4.2 Subject-matter entitled to the filing date 7 May 1984; i.e. compounds in which the symbols R_5 and R_6 represent hydrogen atoms.

4.2.1 The closest prior art to this subject-matter is considered to be document (1) which was published on 30 November 1983. This document discloses 3,4-dihydro-2H-benzo[b]-pyran-3-ols, and esters and ethers thereof and 2H-benzo-[b]pyrans having antihypertensive activity. These compounds are substituted in the 4-position by a radical of the formula R_8-N-CX-R_7, wherein R_7 is a hydrogen atom or a C_{1-6} alkyl optionally substituted by a hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl or carboxy radical, or a C_{1-2} alkyl radical substituted by halogen or a C_{2-6} alkenyl radical, R_8 is a hydrogen atom or a C_{1-6} alkyl and X is

oxygen or sulphur; this group being trans to the group at the 3-position when there is no double bond between the 3- and 4-positions (cf. Claim 1 in combination with page 18, lines 9 to 12).

4.2.2 In the light of this closest prior art the technical problem underlying the application is to provide further benzo[b]pyrans having antihypertensive activity. According to the application this technical problem is essentially solved by providing 3,4-dihydro-2H-benzo[b]pyrans substituted at the 4-position by a radical of the formula R_8-N-CX-R_7, wherein R_7 is amino optionally substituted by a C_{1-6} alkyl group or a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen, or a C_{1-6} alkoxy group or a phenoxy group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; R_8 is a hydrogen atom or a C_{1-6} alkyl and X is oxygen or sulphur.

4.2.3 Document (10) discloses that similarly substituted 3,4-dihydro-2H-benzo[b]pyrans and 2H-benzo[b]pyrans possess antihypertensive activity. The teaching of this document combined with that of document (2) referred to above establishes that the antihypertensive activity is retained independent of whether the nucleus is a 3,4-dihydro-2H-benzo[b]pyran (i.e. R_5 is a hydrogen atom), a 2H-benzo[b]pyran (i.e. R_5 and R_6 together represent a bond) or a 3,4-dihydro-2H-benzo[b]pyran-3-ol (i.e. R_5 is a hydroxy group and R_6 is a hydrogen atom).

In these circumstances, it has to be decided whether the skilled person would have expected that compounds in which the 4-substituents present in the compounds of document (1) have been replaced by the present groups would possess antihypertensive activity.

4.2.4 Document (7) discusses the theory of bioisosterism and its use in drug design. On page 565 of this paper it is stated that in making a bioisoteric replacement certain parameters of the group being charged could be considered:

(a) size, (b) shape (bond angles, hybridisation), (c) electronic distribution (polarisability, inductive effects, charge, dipole), (d) rapid solubility, (e) water solubility, (f) pKa, (g) chemical reactivity (including likelihood of metabolism), and (h) hydrogen bonding capacity.

Table 4 (cf. pages 573 to 580), which lists some examples of biosterism, contains no examples involving a 2H-benzo[b]pyran nucleus or any reference to compounds having antihypertensive activity. Therefore, at most this document could be considered as providing some general guidance to the skilled person involved in research in the pharmaceutical field, but no pointer in the direction of the proposed solution to the present technical problem.

4.2.5 Therefore, in the Board's judgement, the cited prior art does not contain any teaching which would have led the skilled person to expect that the present technical problem would be solved by the present compounds. Thus, the subject-matter entitled to the filing date also involves an inventive step.

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 10 filed on 9 June 1989 subject to the correction of Claim 5 referred to in paragraph 2 above.

The Registrar

E. Görgmaier

The Chairman

K.J.A. Jahn