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D E C I S I O N
of 8 March 2000

Case Number: T 0546/97 - 3.3.1

Application Number: 92104830.2

Publication Number: 0498466

IPC: C07D 451/12

Language of the proceedings: EN

Title of invention:
Indazole-3-carboxamide and -3-carboxylic acid derivatives

Applicant:
BEECHAM GROUP PLC

Opponent:
-

Headword:
Indazole derivatives/BEECHAM

Relevant legal provisions:
EPC Art. 56, 76(1), 78(1)(b), 123(2)
EPC R. 27

Keyword:
"Inventive step (yes) - non-obvious solution"

Decisions cited:
T 0689/90

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0546/97 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 8 March 2000

Appellant: BEECHAM GROUP PLC
Four New Horizons Court
Harlequin Avenue
Brentford
Middlesex TW8 9EP (GB)

Representative: Tocher, Pauline
SmithKlein 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 6 March 1997 refusing European patent application No. 92 104 830.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. F. Ranguis
R. T. Menapace

Summary of Facts and Submissions

i. This appeal lies from the decision of the Examining Division posted on 6 March 1997 to refuse the European patent application No. 92 104 830.2 (publication No. 0 498 466), which is a divisional application of the earlier application No. 86 302 964.1, on the ground that at least part of the then pending:

Claims 1 to 10

did not involve an inventive step contrary to the requirement of Article 56 EPC in the light of the disclosure of documents:

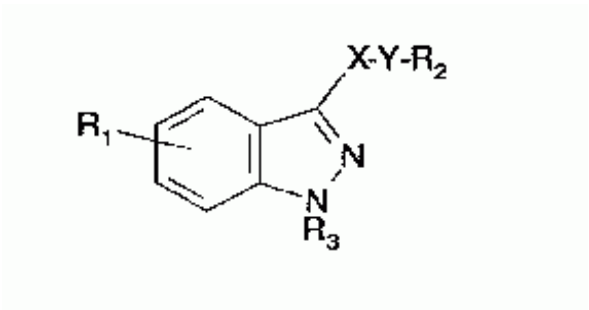
(1) WO-A-85/01048,

(2) WO-A-84/00166,

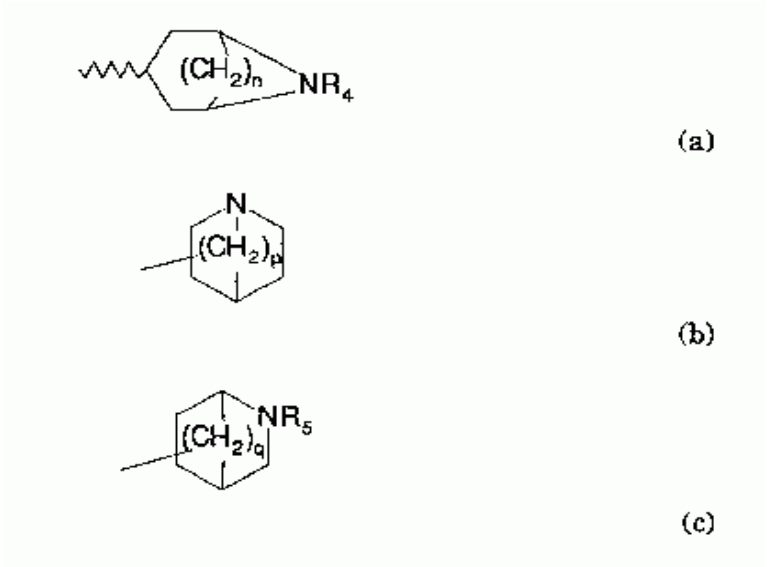
(3) Arch. Int. Pharmacodyn. **1961**, CXXXIII, No. 1-2, 138ff.

1. Independent Claim 1 reads as follows:

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



wherein
X is CO and Y is NH or O
R_3 is hydrogen, C_{1-6}alkyl, C_{3-7}alkenyl-methyl, phenyl or phenyl C_{1-4}alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6}alkoxy or C_{1-6}alkyl;
R_1 is hydrogen, halogen, CF_3, C_{1-6}alkyl or C_{1-6}alkoxy;
R_2 is a group of formula (a), (b) or (c):



wherein n is 2 or 3;
p and q are independently 1 to 3;
and
R_4 or R_5 is C_{1-3} alkyl."

Independent Claim 8 is worded as follows:

"A compound of formula (1) wherein R_2 is of formula (a) or (c) as defined in claim 1, but wherein R_4 or R_5 is replaced by hydrogen".

Independent Claims 9 and 10 relate, respectively, to

pharmaceutical compositions comprising a compound according to any one of Claims 1 to 7 and to the use of a compound according to Claims 1 to 7 in the manufacture of a medicament for use as a 5-HT antagonist.

III. As to the description, the present (divisional) application contained merely the following text:

"This invention relates to novel compounds having pharmacological activity, to processes for their preparation and their use as pharmaceuticals.

This is a divisional application of European Patent Application No. 86302964.1 in the name of Beecham Group p.l.c. (EP publn No. 200444), the subject matter of which is wholly incorporated herein by reference.

This invention is described with reference to EP-A-200444 and the claims which follow."

IV. In its decision, the Examining Division held that the solution to the problem of providing further compounds having 5-HT antagonistic activity was prima facie obvious. First, it was clear from documents (1) and (2) that the aryl or heteroaryl group attached to the azabicycle could be varied to a considerable extent while maintaining the qualitative 5-HT-antagonist properties of the resulting compounds. This finding was, furthermore, confirmed by the disclosure of document (3) which showed that on exchange of indole for indazole, the antagonist activity on 5-HT receptors was maintained. It was the Examining Division's conclusion that the skilled worker facing with the problem of designing new 5-HT antagonists would have

inevitably expected upon exchange of indole for indazole in a known substituted azabicyclic compounds to obtain compounds which exhibit 5-HT antagonist activity.

In addition, the Examining Division found that an improved activity could not be established for all the compounds encompassed by Claim 1.

As an obiter dictum, the Examining Division observed that Claim 8 extended beyond the content of the parent application and hence contravened Article 76(1) EPC.

V. At the oral proceedings held before the Board of Appeal on 8 March 2000, the Appellant, upon having made aware by the Board of another possible objection under Article 84 EPC regarding the expression "is replaced by hydrogen" present in Claim 8, submitted as sole request a new set of Claims 1 to 10 differing from the previous one in that the Claim 8 was worded as follows:

"A compound of formula (1) wherein R_2 is of formula (a) or (c) as defined in claim 1, but wherein R_4 or R_5 **represent** hydrogen".

VI. The Appellant's submissions both in the written procedure and at the oral proceedings can be summarised as follows:

- the current Claim 8 satisfied the requirements of Articles 76(1) as it was supported by the description of the earlier application as filed. The said description indicated that the compounds of formula (VII) as set out pages 15 and 16 formed an aspect of the invention, the side chain X-Y-R_2

being preferably in position 3, Z being often NR_3 and R_a being not present.

- regarding inventive step of the Claim 1, the document (3) could not be regarded as a relevant prior art given that the disclosed indazole derivatives showed no or at best a low 5-HT antagonist activity and therefore did not aim at the same objective as the claimed subject-matter. Documents (1) or (2), although teaching a number of possibilities, including indole, for a moiety in a chemical compound having 5-HT antagonistic activity, would not have rendered obvious further possibilities. A prima facie case of obviousness was therefore not established.

VII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 to 10 as submitted during the oral proceedings of 8 March 2000.

VIII. At the end of the oral proceedings the decision of the Board was given orally.

Reasons for the Decision

1. The appeal is admissible.

2. *Content of the application - Articles 123(2), 76(1), 78(1)(b) EPC*

2.1 The statement in the text of the present (divisional) application as filed (see point III, above) is clear and unambiguous in the sense that the entire text of

the description of the earlier application n°86302964.1, published under EP-A-200444, is incorporated by reference so that the description of the present application shall be identical to the original text of the description of the earlier application referred to. This text as such fulfills the requirements set out in decision T 689/90 (OJ EPO 1993, 616, point 2.2 of the reasons; Guidelines C-II, 4.18) and the Board sees no reason why such an incorporation by reference should not be valid and acceptable, given that it is permissible and widespread practice to file divisional applications with a text of the description identical to that of the earlier application.

2.2 Nonetheless, in order to comply with Rule 27 EPC and to allow amendments of the text of the description, and in general, in order to render the patent specification, regarding the essential features of the invention, self-contained (Article 78(1)(b) EPC, cf. Guidelines above and C-VI, 9.5) , it will be necessary - as the applicant has been invited to in the Examining Division's communication dated 7 November 1994 - to expressly incorporate those parts of the description referred to which are relevant for the subject-matter claimed in the present application. But this can be left to a later stage after the patentability of the subject matter claimed has been examined on the basis of the text of the description of the earlier application which forms part - actually the whole substantive part - of the description of the present application (Article 78(1)(b) EPC) and, therefore has to be taken into account for the purposes of Articles 76(1) and 123(2) EPC.

2.3 In the Board's judgment, Claim 1 does not contravene

the requirement of Article 76(1) EPC as it does not amount to an inadmissible singling out of a specific sub-class of compounds not disclosed in the earlier application but, on the contrary, amounts to a limitation of the possibilities already disclosed in the earlier application, i.e. to a limitation of the scope of the said application. The reasons for this finding are as follows.

Referring to the content of the earlier application, the Board first notes that the group X-Y-R_2 is preferably in position 3 (R_b is not present) (see page 2, lines 10 to 11; page 4, lines 16 to 18) and preferably X is CO and Y is NH or O (see page 3, line 31). Furthermore, the groups R_4, R_5 present when R_2 is the group (a) or (c) are preferably C_{1-7} alkyl, including as groups "of interest", C_{1-3} alkyl such as methyl, ethyl and n- and iso-propyl (see page 4, lines 33 to 35). Z is often NR_3 and R_a is not present (see page 3, line 33). The expression "often", although less strong than "preferred" distinguishes, nevertheless, in the present context, those groups from the others. The sole amendment which is not supported by a distinguishing expression in the description relates to the group R_1. However, the list of the five selected substituents (hydrogen, halogen, CF_3, C_{1-6}alkyl or C_{1-6}alkoxy) present in the Claim 1 results from a simple limitation of a longer list such as set out page 2, lines 14 to 24. The deletion of the other substituents does not therefore lead to an undisclosed combination of specific meanings.

The Board concludes from the above that the present Claim 1 is directly and unambiguously derivable from the earlier application as filed and thus complies with

the requirement of Article 76(1).

2.4. Likewise, Claim 8 is supported by the earlier application as filed given that the compounds of formula (VII) are said to "form an aspect of the invention" (see page 20, lines 19 to 20) and, therefore, comprise the specific embodiments related to the description of compounds of formula (I) (see point 2.3 above).

3. *Novelty - Article 54(1) and (2) EPC*

3.1 After examination of the cited prior art documents, the Board has reached the conclusion that the subject-matter as defined in the claims as granted is novel. Since novelty had never been contested by the Examining Division, it is not necessary to give reasons for this finding.

4. *Inventive step*

4.1 It remains to be decided whether or not the present request involves an inventive step as required by Article 56 EPC. In accordance with the "problem-solution approach" consistently applied by the Boards of Appeal to assess inventive step on an objective basis, it is necessary to establish the closest prior art being the starting point, to determine in the light thereof the technical problem which the invention addresses, to verify that the technical problem is solved by all the embodiments encompassed within the claimed solution and to examine whether the claimed solution is obvious or not in view of the state of the art.

4.2 The patent in suit relates to compounds having a 5-HT antagonist activity in which an azabicyclic moiety is attached to an indazole moiety through an ester or amide link. Those compounds are used in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis (see page 24, lines 1 to 6).

Document (3) relates to a general study about 5-hydroxytryptamine (5-HT) like substances, namely indolealkylamines or indazolealkylamines. The aim of this publication is to study the 5-HT like action (stimulant activity) or the anti-5-HT action (antagonistic activity) of those substances. From the examples indicated in Table II, pages 150 and 151, it turns out that the indazolealkylamines have either a stimulant activity and no antagonistic activity (examples 51 to 57) or a low antagonistic activity (examples 58 and 60). Furthermore, examples 58 and 60 appear to be less relevant than examples 51 to 57 as they are structurally more remote from the claimed compounds since they present a benzyloxy substituent attached to the phenyl ring. In addition, the conclusions of this study confirm the lack of significant anti-5-HT action of the indazolalkylamines and in general of the tested substances as follows:

"k) Indazolealkylamines, as already observed by Ainsworth (1958) showed a remarkable 5-HT like activity," (see page 154, fourth paragraph).

"5. If present, the antagonistic activity of the examined compounds was rather low, especially when assayed on the rat uterus preparation." (see page 154, bottom paragraph),

"None of the examined compounds had marked antagonistic activity." (see page 155, third and fourth lines from the bottom).

It can be concluded that this document does not aim at the same objective as the patent in suit and, therefore, cannot be regarded as the closest state of the art for assessing inventive step.

Document (2) relates to compounds having a 5-HT antagonist activity in which an azabicyclic moiety is attached to an indole moiety through an ester or amide link (see pages 3 to 4 and page 44, lines 12 to 13). Numerous examples are disclosed in support of the scope of the general formula related to those derivatives. In particular, the Board notes that example A-2 (see page 25) describes the indol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1] oct-3-yl-ester or ICS 205-930 or Tropisetron, one of the two most preferred compounds (see page 48, lines 17 to 19), which, furthermore, according to the Appellant, represents a significant advance in 5-HT_3 receptor antagonist activity (see page 3 of the submissions dated 21 January 1992, filed in the course of the examination proceedings by a letter dated 12 May 1995). There are also many other examples of derivatives which differ from the claimed subject-matter in that they possess an indole moiety in lieu of an indazole one.

This document aims at the same objective as the claimed invention and differs therefrom solely in that the derivatives comprise an indole moiety.

Document (1) relates to compounds having an 5-HT antagonist activity in which an azabicylic moiety is

attached to an aryl or heteroaryl moiety through an ester or amide link. This document was filed 14 months later than document (2) and it represents a generalisation of the disclosure of document (2). In particular, the heteroaryl moiety which is limited to indole moiety in document (2) is extended, in document (1), in addition to indole, to quinolynil, pyridyl or 2H-1-benzopyranyl moiety (see claim 1).

The disclosure of this document aims at the same objective as the claimed invention and differs therefrom solely in that the derivatives comprise an indole, quinolynil, pyridyl or 2H-1-benzopyranyl moiety in lieu of an indazole moiety.

The Board concurs with the Examining Division and the Appellant that either document (1) or (2) may represent the closest state of the art. Nevertheless, document (2) contains much more information due to the greater number of examples (see pages 22 to 44) and moreover describes the Tropisetron (see page 25), the most significant 5-HT_3 receptor antagonist, and represents, therefore, the most promising spring-board towards the claimed invention which was available to the skilled person. In any case, electing document (1) as the closest state of the art would not have changed the final conclusion of the Board.

4.3 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 compounds having an 5-HT antagonist activity comprising both an azabicyclic moiety and an heteroaryl moiety.

4.4 In view of the pharmacological tests related to the evaluation of the compounds No. 1 to 3, 5, 8, 10 and 11 for antagonism of the von Bezold-Jarish reflex reported page 37 of the earlier application, the Board is satisfied that the compounds as defined in Claim 1 solve the said technical problem.

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

The Examining Division held that in the light of the disclosures of the documents (1), (2) and (3) "the skilled worker who was aware of the prior art and faced with the problem of designing new 5-HT antagonists would inevitably have expected upon exchange of indole for indazole in a known substituted azabicyclic compound to obtain compounds which exhibit, on a qualitative basis, 5-HT antagonistic activity: the claimed solution is therefore considered to be *prima facie* obvious.

In the Board's judgment, this line of arguments falls on the fact that the authors of document (3) which studied the 5-HT stimulant and antagonistic activity of various indole or indazole derivatives concluded that indazole compounds have no or a low antagonistic activity (see point 4.2 above).

Therefore, the person skilled in the art, in view of the teaching of documents (1) and (2) would not have considered the claimed indazole derivatives as he would not have expected, given the teaching of document (3), that such imidazole derivatives show an anti-5-HT activity.

5. It follows from the above that the subject-matter of Claim 1 is not rendered obvious by the cited prior art. The same applies to the dependent Claims 2 to 7 relating to specific embodiments of said independent Claim 1.

Independent Claim 8 (see point II above) relates to compounds which, according to the description of the application, are useful as intermediates to prepare the compounds of claims 1 to 7 (when R_1 is not halogen) through a process route involving hydrogenolysis of compounds of formula (I) wherein R_4 or R_5 are benzyl, set out in the application but no longer claimed here, followed by alkylation of the intracyclic amino group. The subject-matter of this claim is supported by the inventive concept underlying Claim 1 as it takes part in an analogy process for the preparation of the compounds of Claim 1, it is not suggested by the state of the art and provides non obvious essential structural elements of the compounds of Claim 1.

Independent Claim 9 relating to a pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and independent Claim 10 relating to the use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for use as a 5-HT antagonist are based on the same inventive concept and derive their patentability on the same basis as does Claim 1.

6. As a result, the Board comes to the conclusion that the claimed subject-matter complies with the requirements of Article 52(1) EPC and a patent can be granted

provided the other requirements for grant are met, here in particular the express incorporation of the relevant parts of the text of the description from the (earlier) application published as EP-A-200444 (see point 2.2 above). To this end the case is remitted to the first instance (Article 111(1) EPC).

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 with the order to grant a patent with the Claims 1 to 10 submitted on 8 March 2000 and a description to be adapted.

The Registrar: The Chairman:

N. Maslin A. Nuss