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Datasheet for the decision of 31 May 2007

Case Number: T 0315/05 - 3.3.01

Application Number: 96943218.6

Publication Number: 0874823

IPC: C07D 213/30

Language of the proceedings: EN

Title of invention:
Tri-substituted phenyl derivatives useful as PDE IV inhibitors

Applicant:
Celltech R&D Limited

Opponent:
-

Headword:
PDE IV Inhibitors/CELLTECH

Relevant legal provisions:
EPC Art. 54, 56, 123(2)

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

Decisions cited:
-

Catchword:
-

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Case Number: T 0315/05 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 31 May 2007

Appellant: Celltech R&D Limited
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Representative: Marsden, John Christopher
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 October 2004 refusing European application No. 96943218.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: C. M. Radke
J. Van Moer

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division dated 19 October 2004, by which the European Patent Application no. 96 943 218.6 (published as WO-A-97/23 460) was refused.

II. The following documents were cited during the examination and appeal proceedings:

(D1) WO-A-94 20 446
(D2) WO-A-95 17 386
(D3) WO-A-94 14 742
(D4) WO-A-95 35 281 (cited as prior art under Article 54(3) EPC).

III. The Examining Division deemed the comparative test described on page 30 of the specification not to be relevant as it did not compare the compounds claimed with that of the closest prior art, i.e. with the product of example 32 of document (D3). So the problem to be solved could only be considered as to provide alternative agents inhibiting phosphodiesterase (PDE) isoenzymes of type IV. In particular, documents (D2) and (D3) disclosed a plurality of such agents which are trisubstituted phenyl derivatives having a wide variety of aryl substituents. The Examining Division concluded that the solution of the problem by providing the compounds claimed was obvious to the skilled person and that the subject-matter of the claims was not based on an inventive step.

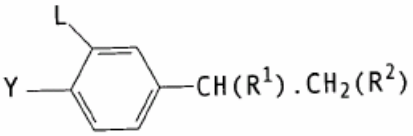
IV. In reply to the Board's communications dated 16 August 2006 and 7 February 2007, the Appellant finally

submitted a set of claims to meet the grounds for refusal and the objections raised by the Board.

The claims on file are claims 1 to 10 filed with the letter dated 8 May 2007.

The independent claims 1 and 10 read as follows:

" 1. A compound of formula (1):



(1)

wherein:

Y is a halogen atom, a C_{1-6} alkyl group or a group $-XR^a$ group in which X is -O-, $-S(O)_p-$ [where p is zero or an integer of value 1 or 2] or $-N(R^b)-$ [where R^b is a hydrogen atom or a C_{1-6} alkyl group] and R^a is a hydrogen atom or an C_{1-6} alkyl group optionally substituted by 1, 2 or 3 fluorine or chlorine atoms;

L is a group -XR where X is as defined above and R is a C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group;

R^1 is a group -Ar.NH.CO.NH.Alk.Ar, $-Ar.CH_2.NH.CO.NH.Alk.Ar$, -Ar.CO.Alk.Ar, $-Ar.CH_2.CO.Alk.Ar$, $-Ar.NH.SO_2.NH.Alk.Ar$, $-Ar.CH_2.NH.SO_2.NH.Alk.Ar$, $-Ar.NH.SO_2.Alk.Ar$, $-Ar.CH_2.NH.SO_2.Alk.Ar$, $-Ar.N(CH_3).CO.NH.Alk.Ar$, $-Ar.CH_2N(CH_3).CO.NH.Alk.Ar$, $-Ar.N(CH_3).SO_2.NH.Alk.Ar$ or $-Ar.CH_2.N(CH_3).SO_2.NH.Alk.Ar$

where Alk is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_q-$ or $-N(R^b)-$ groups [where q is 1 or 2 and R^b is as defined above] and each Ar is a phenyl group optionally substituted by halogen atoms, C_{1-6} alkyl, C_{1-6} haloalkyl, amino, methylamino, ethylamino, dimethylamino, nitro, $-NH.SO_2.NH_2$, $-NH.SO_2.NH.CH_3$, $-NH.SO_2.N(CH_3)_2$, $-NH.CO.CH_3$, $-NH.CO.NH_2$, $-N(CH_3).CO.NH_2$, $-NH.CO.NH.CH_3$, $-NH.CO.NH.CH_2.CH_3$ or $-NH.CO.N(CH_3)_2$ groups, each of said atoms or groups being optionally separated from the phenyl group by a $-CH_2-$ group;

R^2 is a group Ar' where Ar' is a C_{6-12} monocyclic or bicyclic aryl group or a C_{1-9} monocyclic or bicyclic heteroaryl group containing one to four heteroatoms selected from oxygen, sulphur and nitrogen atoms;

and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

10. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 together with one or more pharmaceutically acceptable carriers, excipients or diluents."

V. The Appellant argued that the result of the comparative tests indicated on page 30 of the present application showed that the claimed compounds exhibit an improved metabolic stability with respect to the compounds known from the prior art. He considered this effect to be surprising and concluded that the subject-matter of the claims was based on an inventive step.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted based on the following documents:

Description

Pages 1, 20-22 and 26-30 as originally filed;
pages 2, 2a, 4, 9, 10, 15, 18, 19 and 23-25, filed with the letter of 10 June 2003;
pages 8 and 2b, filed with the letter of 27 December 2006;
5-7, 14, and 16, filed with the letter of 17 April 2007,
with pages 3, 11-13 and 17 cancelled.

Claims

Claims 1 to 10 filed with the letter of 8 May 2007.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC*

Present claim 1 has its basis in claims 1 to 3 as originally filed, and in the description as originally filed on page 4, lines 24-30 and page 5, lines 5-7 (the number of carbon atoms in the alkyl groups Y or L); page 16, lines 9-11 (the optional substituents of the alkyl group Y), page 5, lines 14-16 and page 6, lines 14-17 (the number of carbon atoms of the alkenyl, cycloalkyl or cycloalkenyl groups L); page 19, lines 5-25, page 7, lines 31-34, page 9, lines 6-8 and page 11, lines 8-13 (the definition of the group Ar); page 19, lines 5-7 and page 7, line 31, to page 8, line 6 (the definition of R^2) of the application as originally filed.

Claims 2 to 7, 9 and 10 have their basis in claims 4, 6-9, 12, 14 and 15 as originally filed, where the number of carbon atoms in the alkyl group R^a in claim 3 is disclosed on page 4, lines 24-27 and the number of carbon atoms in the cycloalkyl group R in claim 5 is disclosed on page 6, lines 14 and 15, of the application as filed.

Claim 8 is based on page 17, line 10, of the application as filed.

Hence, the Board is satisfied that the amendments do not contravene the requirements of Article 123(2) EPC.

3. *Novelty*

The Examining Division considered the subject-matter claimed to be novel (see point 2 of the reasons of the decision under appeal). The Board is satisfied that this is the case because said subject-matter differs from the closest compounds of the prior art in that these do not have a radical R^1 according to formula (1) as defined in present claim 1, where said radical has a terminal -Alk-Ar group (see, e.g., example 32 of (D3) and the last compound mentioned in claim 9 of (D4)).

4. *Inventive step*

4.1 In accordance with the "problem-solution" approach consistently applied by the Boards of Appeal, it is necessary, as a first step, to establish the closest state of the art which is normally a prior art document disclosing subject-matter aiming at the same objective

as the claimed invention and having the most relevant technical features in common.

4.2 The Board agrees with the Examining Division in that document (D3), especially the product of its example 32, represents the closest prior art (see point 4.2 of the decision under appeal).

Said example discloses the preparation of N-{4-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl] phenyl} N'-ethylurea. This product differs from the ones claimed in present claim 1 in that it has an ethylurea group at a position in the molecule where present claim 1 requires an aralkylurea group (see the definition of radical R^1 in present claim 1).

4.3 The least ambitious problem to be solved by the subject-matter claimed may be considered as providing alternative compounds which are useful as PDE-IV inhibitors. This problem has indeed been solved as is apparent from present examples 1 and 2.

4.4 It has now to be determined if the prior art renders the solution provided in the present claims obvious.

In example 32 of document (D3), the product bears a phenyl-N'-ethylurea group at the carbon atom in the α-position to the trisubstituted benzene ring, said group corresponding to the radical R^4 as defined in this document, which may be a radical -Ar, where Ar in turn may be substituted by radicals R^{10} (see page 5, lines 4-5 and page 6, lines 11-24). The definition of the substituents R^{10}, however, excludes terminal aryl radicals as are required in radical R^1 as defined in

present claim 1. Hence, document (D3) as such cannot render the subject-matter of the present claim obvious.

The same applies to document (D2) where the radical R^3 (which corresponds to radical R^4 in document (D3)) is defined as R^4 in (D3) (see (D2), formula (2) on page 2 and page 9, lines 13-25).

In document (D1) the radicals R^3 and R^6 at the carbon atom in the α-position to the trisubstituted benzene ring are defined as follows:

R^3 may be hydrogen, optionally substituted alkyl, $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ (see page 2, formula (1) and lines 30-34);
R^6 may be a hydrogen atom or a hydroxyl group (see page 3, line 5).

Hence, the definitions of R^3 and R^6 in (D1) differ from the definition of R^1 in present claim 1 at least in that they are not bonded to that position via an arylene group.

Consequently, also document (D1) does not give any indication that

- the ethylurea group in the product of example 32 of document (D3), if replaced by an aralkylurea group,

or, more generally,

- the modification of the compounds disclosed in document (D3) by replacing radical R^4 by a radical of one of the following formulae
  -Ar-NH-CO-NH-Alk-Ar ,

-Ar-CH_2-NH-CO-NH-Alk-Ar ,
-Ar-CO-Alk-Ar ,
-Ar-CH_2-CO-Alk-Ar ,
-Ar-NH-SO_2-NH-Alk-Ar ,
-Ar-CH_2-NH-SO_2-NH-Alk-Ar ,
-Ar-NH-SO_2-Alk-Ar ,
-Ar-CH_2-NH-SO_2-Alk-Ar ,
-Ar-N(CH_3)-CO-NH-Alk-Ar ,
-Ar-CH_2-N(CH_3)-CO-NH-Alk-Ar ,
-Ar-N(CH_3)-SO_2-NH-Alk-Ar or
-Ar-CH_2-N(CH_3)-SO_2-NH-Alk-Ar,
in which Ar means an optionally substituted phenyl group,

will provide alternative compounds useful as PDE-IV inhibitors.

Document (D4) belongs to the state of the art under Article 54(3) EPC and thus cannot be used when assessing inventive step.

Consequently, none of the cited prior art documents alone or in combination can render the subject-matter of the present claim 1 obvious.

The same applies to the subject-matter of dependent claims 2-9 and to the subject-matter of claim 10 which is directed to a pharmaceutical composition containing a compound as defined in any of the claims 1-9.

Hence, the subject-matter of the present claims is based on an inventive step.

5. The Appellant provided a description adapted to the amended claims. The Board is satisfied that this adapted description satisfies the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent in the following version:

Description

Pages 1, 20-22 and 26-30 as originally filed.
Pages 2, 2a, 4, 9, 10, 15, 18, 19 and 23-25, filed with the letter of 10 June 2003.
Pages 8 and 2b, filed with the letter of 27 December 2006.
Pages 5-7, 14, and 16, filed with the letter of 17 April 2007.

Claims

No. 1 to 10 filed with the letter of 8 May 2007.

The Registrar: The Chairman:

N. Maslin A. Nuss