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Datasheet for the decision of 7 December 2007

Case Number: T 0136/05 - 3.3.02

Application Number: 96932197.5

Publication Number: 0852499

IPC: A61K 31/70

Language of the proceedings: EN

Title of invention:
Therapeutic azide compounds

Applicant:
UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. AND EMORY UNIVERSITY

Opponent:
-

Headword:
6-Azidopurine prodrugs/UNIVERSITY OF GEORGIA RESEARCH FOUNDATION

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

Keyword:
"Amended claims at appeal: novelty (yes), specific compounds; inventive step (yes), non-obvious solution"

Decisions cited:
-

Catchword:
-

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Case Number: T 0136/05 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 7 December 2007

Appellant: UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. AND EMORY UNIVERSITY
D.W. Brooks Drive
Athens
GA 30602-7411 (US)

Representative: Fisher, Adrian John
CARPMAELS & RANSFORD
43-45 Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 24 August 2004 refusing European application No. 96932197.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

I. European patent application No. 96 932 197.5 was filed as international patent application WO 97/09052.

II. The following document are relevant for the present decision:

(1) E. Kojima et al., Nucleic acids symposium series, 1991, (25), 91-92
(2) G.H. Hakimelahi et al., J. Sci. I. R. Iran, 1990, 1(3), 192-196
(3) EP-A-0 400 686
(4) T. Koudriakova et al., J. Med. Chem. 1996, 39(23), 4676-4681
(5) K.R. Svendsen et al., Cancer Chemother. Pharmacol. 1992, 30, 86-94
(6) K. Shanmuganathan et al., J. Med. Chem. 1994, 37, 821-827
(7) R. Whitley et al., Drugs, 1980, 20, 267-282
(8) G. Darby, Antivir. Chem. Chemother. 1995, 6(Suppl. 1), 54-63

III. The present appeal lies from a decision of the examining division refusing the application under Article 97(1) EPC 1973 pursuant to the requirements of Articles 54(1), (2) EPC 1973.

The decision was based on claims 1 to 9 filed with the letter of 11 December 2002. Claim 1 read as follows:

"1. A prodrug form of a therapeutically active purine, pyrimidine, nucleoside or phosphorylated nucleoside, said prodrug comprising an azide moiety which is

converted *in vivo* to an amino, carbonyl or hydroxyl moiety of said therapeutically active compound."

The examining division considered that the subject-matter of claims 1, 2, 8 and 9 did not fulfil the requirements of novelty under Article 54(1), (2) EPC 1973.

In particular, the examining division noted that compound **22** disclosed in document (1) comprised all the structural features shared by the preferred compounds claimed in the application in suit, namely, a purine ring functionalised by an azido group in position 6. The examining division was therefore of the opinion that compound **22** could be assumed to be a prodrug capable of being converted *in vivo* into the corresponding therapeutically active amino and hydroxyl derivatives **16** and **17** disclosed in the same document. Since the applicant had failed to provide any evidence to the contrary, the examining division held that document (1) anticipated the subject-matter of claims 1, 2, 8 and 9.

In addition, the examining division considered that specific azide compounds disclosed in documents (2) and (3) destroyed the novelty of the subject-matter of claim 1.

IV. The appellant (applicant) lodged an appeal against this decision, and filed two auxiliary requests with the grounds of appeal.

V. In the communication sent as an annex to the summons to oral proceedings, the board expressed its preliminary

opinion that the requests on file failed to meet the requirements of Articles 123(2) and 84 EPC 1973.

In addition, the board gave a provisional opinion on the issue of novelty with respect to the subject-matter of the main request. In this context the board noted that a Supplementary Partial European Search Report had been issued for the present application, and that documents (1) to (3) did not therefore represent an exhaustive list of prior art documents relevant to the assessment of novelty for the generic compound claims.

VI. In response to the above-mentioned communication, the appellant filed a third auxiliary request with the letter of 20 September 2007.

VII. In a further communication dated 10 October 2007, the board drew the appellant's attention to a number of deficiencies of the newly filed request with respect to the formal requirements of Articles 123(2) and 84 EPC 1973.

VIII. In response to this further communication, the appellant filed with the letter of 7 November 2007 a new main request and withdrew the previous requests on file. In addition, the appellant withdrew its previous request for oral proceedings on condition that the case be remitted to the examining division for further prosecution.

The newly filed main (sole) request was based on seven claims, whereby the two independent claims read as follows:

"1. A compound for use in treating a pathological condition in a patient, said compound being selected from 6-azido-9-(β-D-3'-deoxyribofuranosyl)purine, 6-azido-9-(2',3'-dideoxy-2'-fluoro-β-D-arabinofuranosyl)-purine, 9-(β-D-arabinofuranosyl)-6-azidopurine, 2-amino-6-azido-9-[(2-hydroxyethyoxy)methyl]-purine, 2-amino-6-azido-9-[3,3-di(hydroxymethyl))propyl]-purine, or a monophosphate, diphosphate or triphosphate or pharmaceutically acceptable salt of any of the foregoing.

7. A pharmaceutical composition for treating a pathological condition in a patient, said composition comprising a compound as recited in any preceding claim, and a suitable pharmaceutical carrier."

IX. On 8 November 2007, the board informed the appellant by fax that the oral proceedings due to take place on 29 November 2007 were cancelled.

X. The appellant (applicant) requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the main (sole) request filed with the letter of 7 November 2007, and that the case be remitted to the first instance for further prosecution on the basis of said request.

Reasons for the Decision

1. The appeal is admissible.

2. *Main (sole) request*

2.1 The main request is based on claims 1 to 6 and 22 as originally filed, whereby the five compounds listed in claim 1 correspond to those disclosed in claims 2 to 6 as originally filed.

In addition, several amendments to the chemical names recited in originally filed claims 2 to 6 have been introduced, which can either be regarded as the correction of obvious errors within the meaning of Rule 88 EPC 1973 (Rule 139 EPC 2000), or are allowable restrictions directly based on the corresponding formulae depicted in the application as originally filed (cf. page 21, line 15 to page 23, line 20; page 27, lines 7 to 30 (Example 1); page 33, line 17 to page 34, line 15 (Example 3)).

In particular, the basis for the specification of the locator "9" for the furanosyl residue in the first two compound names listed in claim 1 can be found in the corresponding formulae of the "cordycepin prodrug" (page 27, Scheme 12, bottom right) and of compound 4(FAAddP) (page 34, Scheme 13, bottom right), wherein the respective sugar moieties are attached to position 9 of the purine ring (see also first two formulae (top row) reproduced on page 8 below). This analysis also applies to the compounds of dependent claims 2 and 3.

Similarly, the corrections introduced into the last two compound names listed in claim 1 are based on the formulae depicted in the description as originally filed at the bottom left of Scheme 6 (page 22) and at

the bottom of Scheme 7 (page 23) (cf. also bottom row of formulae depicted on page 8 below). In this context it is noted that, based on the chemical transformations disclosed in Scheme 6, it is clearly apparent that a double bond is missing in the purine ring of the formula of the end compound. This analysis also applies to the compounds of dependent claims 5 and 6.

Hence, the claims against which clarity objections were raised by the board have been adequately amended or deleted (cf. points V and VII above).

Therefore, the subject-matter of the main request meets the requirements of Articles 123(2) and 84 EPC.

2.2 As already noted in the facts and submissions (see point V), a Supplementary Partial European Search Report has been issued for the present application pursuant to Rule 45 EPC 1973. However, it is stated in Sheet C of said search report that "the search has been carried out for those parts of the application which do appear to be clear (and concise), namely on compounds of claims 2—6", i.e. the claims and compounds which provide the basis for the subject-matter now claimed (cf. point 2.1 above).

It can therefore be concluded that a complete search has been carried out for the subject-matter claimed in the main request.

2.3 Documents (1) to (3) do not disclose any of the specific compounds listed in claim 1.

Document (4) was cited in the Supplementary Partial European Search Report as being an intermediate document relevant inter alia for claim 3 as originally filed. However, as becomes evident from the footnote on page 4676 of document (4), the date of advanced publication of the abstract thereof was 1 October 1996, i.e. after the present international filing date of 6 September 1996. Indeed, as shown in the internet homepage of the Journal of Medicinal Chemistry, the actual date of publication of issue 23 was 8 November 1996. Therefore, document (4) does not belong to the state of the art within the meaning of Article 54(2) EPC.

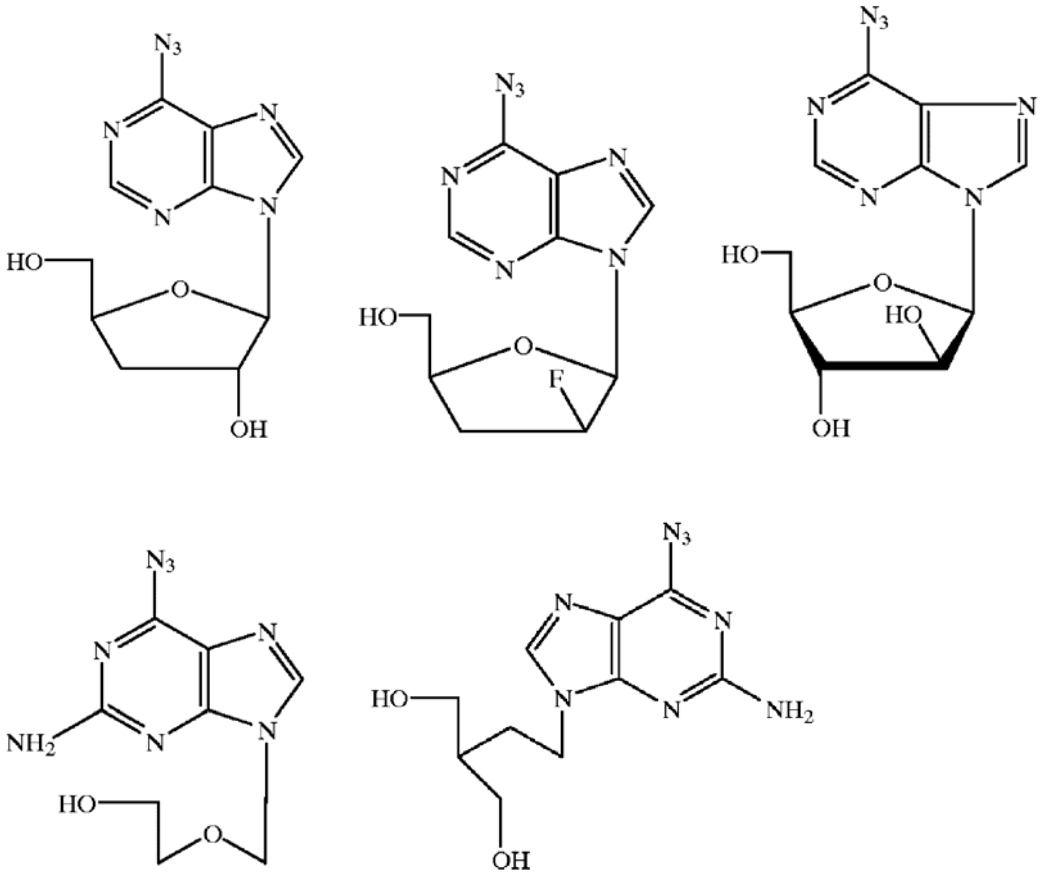
None of the remaining cited prior art documents disclose the specific compounds listed in present claim 1.

The above analysis also applies mutatis mutandis to the pharmaceutical composition according to claim 7.

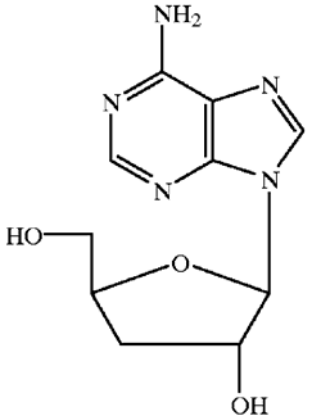
Consequently, the main request meets the requirements of novelty (Articles 52(1) and 54 EPC).

2.4 It remains to be decided whether the subject-matter of the main request involves an inventive step.

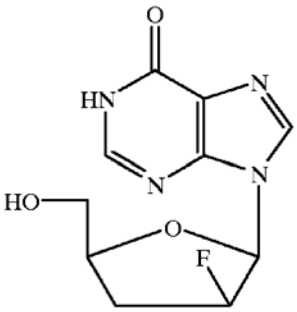
The subject-matter of claim 1 relates to specific 6-azidopurine derivatives (or a monophosphate, diphosphate or triphosphate or pharmaceutically acceptable salt thereof) for use in treating a pathological condition. The formulae corresponding to the chemical names listed in that claim can be depicted as follows:



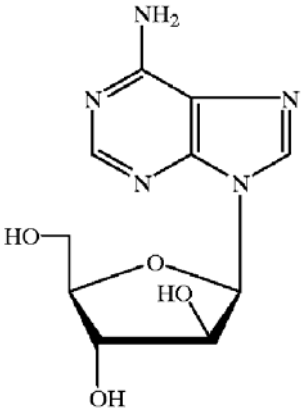
The person skilled in the art at the effective date of the application was aware of documents (5) to (8) cited in the description of the application in suit (see page 7, lines 29 to 31; page 6, lines 28 to 30; page 4, lines 2 to 3; and page 2, lines 22 to 23; respectively). These documents disclose the structurally closest antiviral agents cordycepin, 2'-F-ara-ddI, Ara-A, and acyclovir and penciclovir, respectively, corresponding to the following formulae (cf. also description of application, pages 11, 12 and 45):



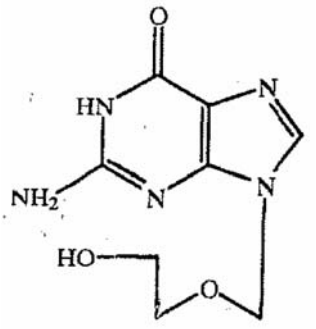
cordycepin



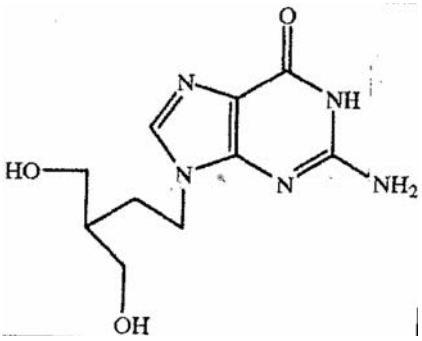
2'-F-ara-ddI



Ara-A



acyclovir



penciclovir

These known active antiviral drugs, which are indicated in the description of the application in suit as being the starting point for determining the problem underlying the invention, do indeed represent the closest prior art.

The problem to be solved consists in providing antiviral nucleoside compounds in a form that increases their half-lives *in vivo* in a warm-blooded animal subject.

The solution as defined in claim 1 relates to the derivatisation at position 6 of the purine ring as an azido group (cf. formulae depicted above).

As the next step it has to be investigated whether the proposed solution solves the problem posed.

According to the application in suit, the claimed 6-azidopurine compounds are transformed *in vivo* to the corresponding active drugs, i.e. cordycepin, 2'-F-ara-ddI, Ara-A, acyclovir and penciclovir, respectively, and provide increased half-lives for the latter (see e.g. page 8, lines 7 to 9; page 9, line 17 to page 12, line 27; claims 14 to 19).

Moreover, experimental results reported in examples 2, 3 and 5 of the description of the application in suit demonstrate by means of *in vivo* tests in mice that the 6-azido derivatives of cordycepin, 2'-F-ara-ddI and Ara-A according to claim 1 are converted to the corresponding parent compounds such that the half-lives of the latter are increased (see, in particular, page 30, line 14 to page 33, line 15; page 40, line 12 to page 44, line 20; and page 49, line 17 to page 53, line 10).

Hence, these test results demonstrate in a plausible manner that the introduction of the azido group at position 6 of the purine ring can be linked to an increase in the half-lives of the corresponding nucleoside analogues bearing a hydroxyl or amino substituent at position 6.

Therefore, in the light of the above, the board is satisfied that the problem has been plausibly solved for all claimed compounds.

Finally, it remains to be investigated whether the proposed solution is obvious to the skilled person in the light of the prior art.

The skilled person starting from the known antiviral nucleoside analogues cordycepin, 2'-F-ara-ddI, Ara-A, acyclovir and penciclovir would have been aware of document (1). This document is directed to a brief study of the synthesis and structure-activity relationships of 2',3'-dideoxypurine nucleosides as potential antiretroviral agents. Amongst the compounds disclosed in document (1) there is one 6-azidopurine nucleoside, namely, compound **22**. The corresponding 6-amino and 6-hydroxy derivatives **16** and **17**, respectively, are also disclosed in document (1). These compounds are all shown to possess excellent activity against rous sarcoma virus as demonstrate in cell tests (page 91, right-hand column, second paragraph).

However, document (1) does not provide any information on the metabolism of compound **22**. Therefore, document (1) does not teach that a 6-azido-purine nucleoside might act as a prodrug for the corresponding amino or hydroxy analogue.

Thus, document (1) does not provide the skilled person with any teaching concerning the derivatisation at position 6 of the known active compounds as the solution to the problem defined above.

Document (2) purely concerns a synthetic study into the coupling reaction of chloromethyl ethers with purine derivatives. Four 6-azidopurine derivatives are disclosed therein (cf. page 194, compounds 9a, 11b, 12b

and 13b). Document (2) contains no information regarding the biological activity or metabolism of these compounds.

Document (3) contains a separate set of claims for the contracting state Austria consisting of three claims: claim 1 relates to a process for preparing purine derivatives of general formula 1, wherein the substituent at position 6 (R^1) may inter alia be azido; claim 2 relates to a process for preparing a pharmaceutical composition which is suitable for treating diseases caused by viruses, which comprises incorporating as active substance a compound of formula 1 which is prepared by the process according to claim 1; and claim 3 relates to a process for preparing medicament formulations for treating diseases caused by viruses, which comprises formulating a compound of formula 1 which has been obtained by the process according to claim 1. Only limited information with respect to the 6-azidopurine compounds can be derived from the remaining disclosure of document (3): processes for the synthesis of the 6-azidopurine derivatives are disclosed on page 3, line 42 and page 4, lines 33 to 36, and a single specific 6-azidopurine derivative is disclosed on page 15 (compound 47), which is structurally further removed from the compounds claimed in claim 1 of the main request than the compounds disclosed in document (1) discussed above.

Therefore, the skilled person would also not be able to extract any valuable teaching from documents (2) and (3) in order to solve the problem posed.

The further prior art documents available in the present case do not come closer to the claimed subject-matter than those addressed above. Hence, the subject-matter of claim 1 of the main request involves an inventive step.

Having regard to the fact that claims 2 to 6 are dependent on claim 1 and that claim 7 is directed to "a pharmaceutical composition … comprising a compound as recited in any preceding claim", it is concluded that the subject-matter of the main and sole request meets the requirements of Articles 52(1) and 56 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 on the basis of the main (sole) request filed with the letter of 7 November 2007 and a description to be adapted thereto.

The Registrar The Chairman

A. Townend U. Oswald