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Datasheet for the decision of 24 March 2023

Case Number: T 0795/21 - 3.3.07

Application Number: 15154759.3

Publication Number: 2955190

IPC: A61P43/00, A61P35/00, C07H19/10

Language of the proceedings: EN

Title of invention:
Chemical compounds

Patent Proprietor:
NuCana plc

Opponent:
Gilead Sciences, Inc.

Headword:
Chemical compounds / NUCANA

Relevant legal provisions:
EPC Art. 56, 76(1)

Keyword:

Inventive step - (no) main request, auxiliary requests 1-3, 10-13, 24-27, 34-37, 48-49, 52-53, 60-61, 54-65, 72-75, 84-87, 96-97, 201-103
Divisional application - subject-matter extends beyond content of earlier application - (yes) auxiliary request 4-9, 14-23, 28-33, 38-47, 50-51, 54-59, 62-63, 66-71, 76-83, 88-95, 98-101, 104-107

Decisions cited:

G 0001/93, G 0001/03, G 0002/10, T 0615/95, T 0859/94, T 0050/97, T 0783/09, T 0948/02, T 0801/02, T 1937/17

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Case Number: T 0795/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 24 March 2023

Appellant: (Patent Proprietor)	NuCana plc 77-78 Cannon Street London EC4N 6AF (GB)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Appellant: (Opponent)	Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 April 2021 concerning maintenance of the European Patent No. 2955190 in amended form.**

Composition of the Board:

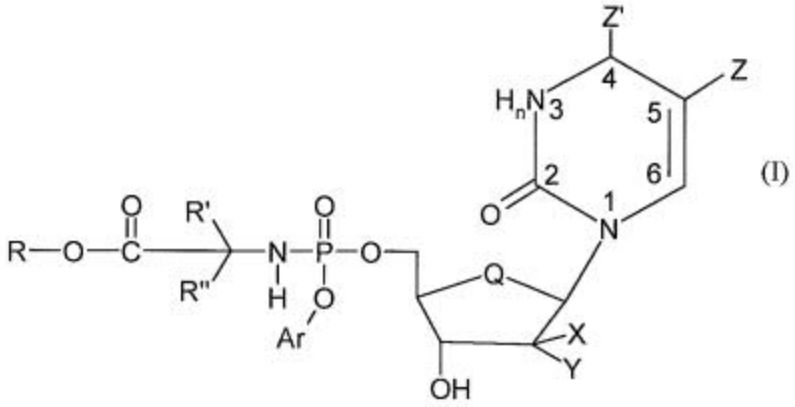
Chairman	A. Usuelli
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 2 955 190 ("the patent") was granted on the basis of fifteen claims.

Independent claim 1 as granted defined:

"A chemical compound having formula I:



(I)

wherein:

R is selected from the group alkyl, aryl and alkylaryl;

R' and R" are independently selected from the group H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;

Q is selected from the group -0- and -CHr;

X is independently selected from the group H, F, Cl, Br, I, OH and methyl (-CH3);

Y is F;

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted;

Z is selected from the group H, alkyl and halogen ; and

n is 0 or 1 ,
wherein when n is 0, Z' is -NH2 and a double bond exists between position 3 and position 4, and when n is 1, Z' is =O;
or a pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula I."

II. The grant of the patent was based on a divisional application from EP04743483.2, which was originally published as WO 2005/012327 A2 ("parent application"). The patent was opposed on the grounds that its subject-matter lacked an inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the (parent) application as filed.

The patent proprietor and the opponent filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with auxiliary request 13 met the requirements of the EPC.

The decision was based on the main request relating to the patent as granted, auxiliary requests 1-6 filed on 6 November 2020, auxiliary requests 7-12 filed on 14 January 2021 and auxiliary request 13 filed during the oral proceedings held on 8 February 2021.

In its decision the opposition division cited *inter alia* the following documents:

D36: US 2003/0109697 A 1
D107: Journal of Medicinal Chemistry 60(13), 2017, 5424-5437

The opposition division arrived at the following conclusions:

(a) The patent as granted did not include subject-matter extending beyond the content of the original disclosure and presented the skilled person sufficient guidance on how to prepare the compounds claimed.

(b) Document D36 represented the closest prior art. Document D107 indicated that a compound covered by formula I was inactive against cancer. The objective technical problem could therefore only be seen in the provision of alternative compounds. As solution to such a trivial problem the claimed subject-matter was obvious. The main request did therefore not meet the requirement of inventive step.

(c) Auxiliary requests 1-12 did not meet the requirement of inventive step for the same reason as the main request.

(d) Auxiliary request 13 complied with Articles 123(2) and 83 EPC. In view of the experimental data on file the objective technical problem was formulated as the provision of alternative compounds with activity against cancer. The claimed compounds were not obvious in view of the prior art. Auxiliary request 13 therefore also complied with the requirement of inventive step.

III. The appellant-patent proprietor filed auxiliary request 1-20 with its statement of grounds of appeal and auxiliary requests 21-108 with its reply to the appeal by the opponent.

Auxiliary request 1 related to the claims as granted except for the deletion of dependent claims 2-12.

Auxiliary request 5 related to the claims of auxiliary request 1 in which the meaning of X is limited to F, Cl, Br, I, OH and methyl ($-CH_3$) by deletion of H.

The extent of the amendments according to each of these auxiliary requests 1-108 with respect to the claims as granted and the relation of these requests to the requests on which the decision under appeal was based is presented in the following tabular summary of these amendments, which was provided by the appellant-patent proprietor in the annex to the reply to the appeal by the opponent:

Summary of amendments made in auxiliary requests

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
1	AR1	AR1	X								
2	AR2	AR2	X	X							
3		AR3	X		X						
4		AR4	X	X	X						
5	AR3	AR5	X			X					
6	AR4	AR6	X	X		X					
7		AR7	X		X	X					
8		AR8	X	X	X	X					
9	AR5	AR9	X			X	X				
10	AR6	AR10	X	X		X	X				
11	AR7	AR11	X					X			
12	AR8	AR12	X	X				X			
13		AR13	X		X			X			
14		AR14	X	X	X			X			
15	AR9	AR15	X			X		X			

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
16	AR10	AR16	X	X		X		X			
17		AR17	X		X	X		X			
18		AR18	X	X	X	X		X			
19	AR11	AR19	X			X	X	X			
20	AR12	AR20	X	X		X	X	X			
21	AR13	N/S	X		X	X	X				
22			X	X	X	X	X				
23			X		X	X	X	X			
24			X	X	X	X	X	X			
25			X						X		
26			X	X					X		
27			X		X				X		
28			X	X	X				X		
29			X			X			X		
30			X	X		X			X		
31			X		X	X			X		
32			X	X	X	X			X		
33			X			X	X		X		
34			X	X		X	X		X		
35			X					X	X		

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
36			X	X				X	X		
37			X		X			X	X		
38			X	X	X			X	X		
39			X			X		X	X		
40			X	X		X		X	X		
41			X		X	X		X	X		
42			X	X	X	X		X	X		
43			X			X	X	X	X		
44			X	X		X	X	X	X		
45			X		X	X	X		X		
46			X	X	X	X	X		X		
47			X		X	X	X	X	X		
48			X	X	X	X	X	X	X		
49			X		X					X	
50			X	X	X					X	
51			X		X	X				X	
52			X	X	X	X				X	
53			X		X			X		X	
54			X	X	X			X		X	
55			X		X	X		X		X	

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
56			X	X	X	X		X		X	
57			X		X	X	X			X	
58			X	X	X	X	X			X	
59			X		X	X	X	X		X	
60			X	X	X	X	X	X		X	
61			X		X				X	X	
62			X	X	X				X	X	
63			X		X	X			X	X	
64			X	X	X	X			X	X	
65			X		X			X	X	X	
66			X	X	X			X	X	X	
67			X		X	X		X	X	X	
68			X	X	X	X		X	X	X	
69			X		X	X	X		X	X	
70			X	X	X	X	X		X	X	
71			X		X	X	X	X	X	X	
72			X	X	X	X	X	X	X	X	
73			X								X
74			X	X							X
75			X		X						X

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
76			X	X	X						X
77			X			X					X
78			X	X		X					X
79			X		X	X					X
80			X	X	X	X					X
81			X			X	X				X
82			X	X		X	X				X
83			X		X	X	X				X
84			X	X	X	X	X				X
85			X						X		X
86			X	X					X		X
87			X		X				X		X
88			X	X	X				X		X
89			X			X			X		X
90			X	X		X			X		X
91			X		X	X			X		X
92			X	X	X	X			X		X
93			X			X	X		X		X
94			X	X		X	X		X		X
95			X		X	X	X		X		X

AR	Referred to in the OD's decision as	Referred to in SoG as	Dependent claims deleted	"A pharmaceutically acceptable salt, ester or salt of such ester" deleted	X is Cl deleted	X is H deleted	X is I or OH deleted	Z is alkyl deleted	*R, Ar, etc. amended*	*X is Br deleted*	*Z is halogen deleted*
96			X	X	X	X	X		X		X
97			X		X					X	X
98			X	X	X					X	X
99			X		X	X				X	X
100			X	X	X	X				X	X
101			X		X	X	X			X	X
102			X	X	X	X	X			X	X
103			X		X				X	X	X
104			X	X	X				X	X	X
105			X		X	X			X	X	X
106			X	X	X	X			X	X	X
107			X		X	X	X		X	X	X
108			X	X	X	X	X		X	X	X

IV. Concerning the documents filed by the parties during the appeal proceedings reference is made to the consolidated list of documents A116-A191, which is available from the register.

The appellant-patent proprietor filed

- document A136 with the statement of grounds of appeal,
- documents A137-A141 with the reply to the appeal by the opponent,
- documents A150-A151 with the letter of 27 September 2022,
- document A152 with the letter of 5 October 2022 and
- documents A180-A190 with the letter of 16 March 2023.

The appellant-opponent filed

- documents A116-A135 with the statement of grounds of appeal,

- documents A142-143 with the reply to the appeal by the proprietor,
- documents A144-149 with the letter of 14 March 2022,
- documents A153-A179 with the letter of 24 February 2023 and
- document A191 with the letter of 21 March 2023.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that

- the submission that a compound such as sofosbuvir, which corresponds to a compound of formula I as defined in the patent in which X/Y represent Me/F, prevents hepatocellular carcinoma as a result of its efficacy in treatment of HCV infection and therefore presents a solution to the problem of preventing cancer was not to be admitted into the appeal proceedings under Articles 12(4) and 12(6) RPBA

- compounds as defined in claim 1 as granted or in any of the auxiliary requests in which X represents H lacked an inventive step in view of the overlap with respect to the disclosure of the compounds in document D36

- the definition of compounds in any of the auxiliary requests which involves the limitation in the meaning of X by the deletion of H singled out a subgroup of compounds which resulted in subject-matter extending beyond the content of the original disclosure.

VI. Oral proceedings were held on 24 March 2023. During the the oral proceedings the appellant-patent proprietor

declared in its opening statement that auxiliary request 1 as filed with the statement of grounds of appeal was its new main request and that the subsequent auxiliary requests on file were renumbered as auxiliary requests 1-107.

VII. The arguments of the appellant-patent proprietor relevant to the present decision are summarized as follows:

(a) Main request - inventive step

Document D36 disclosed phosphoramidate nucleosides with utility in the treatment of a variety of pathologies involving hyperproliferative cells, such as cancer, infectious disease, autoimmune disorder or an inflammatory disorder. The most promising starting point within document D36 was represented by the exemplified compound NB1011 carrying a bromovinyl substitution at the 5-position of the pyrimidine ring and without any substitution at the 2-position of the sugar moiety. Document D36 described this compound as an Enzyme-catalyzed therapeutic agent (ECTA) directed against thymidylate synthetase (TS) having favourable cytotoxicity against tumor cells as compared to normal cells.

The difference between the compounds defined in claim 1 of the main request and NB1011 from document D36 concerned the presence of the substitutions X/Y at the 2-position of the sugar moiety and the absence of the bromovinyl substitution at the 5-position of the pyrimidine.

The patent demonstrated with the experimental results for examples 31, 40 and 41 that compounds as defined in claim 1 of the main request exhibit cytotoxic activity against cancer cells. Relevant cytotoxic activity of the claimed compounds was further substantiated in various post-published documents, including document D107.

In addition, the activity of a compound of claim 1 of the main request such as sofosbuvir against HCV infection, which was reported in document D107, supported the utility of the defined compounds in the prevention of cancer, in particular hepatocellular carcinoma. The issue of prevention of cancer was within the framework of the case presented in the first instance proceedings. The argument concerning cancer prevention would anyway represent a legitimate response to the findings in the decision under appeal and was based on a plausible disclosure in the application as filed.

The objective technical problem should therefore be seen in the provision of further agents with utility in treatment or prevention of cancer.

Document D36 disclosed phosphoramidate nucleosides of a broad general formula which overlapped with the definition of compounds in claim 1 of the main request. Document D36 further referred to the possible utility of the disclosed compounds in treating cancer, infectious disease, autoimmune disorder or an inflammatory disorder.

However, document D36 did thereby not suggest that all compounds covered by the defined general

formula, including the phosphoramidate nucleosides lacking a 5-substitution to the pyrimidine moiety covered by the general formula, would actually be useful in treatment of cancer.

On the contrary, document D36 characterized the therapeutically useful compounds as "5'-phosphoramidatyl 1,**5**-substituted pyrimidines" and referred to these compounds as "ECTA"-compounds. In this context document D36 indicated that such compounds are substituted at the 5-position of the pyrimidine with a group that interacts with an endogenous intracellular enzyme. Document D36 provided no further explanation for the therapeutic activity of the disclosed compounds. The experimental data presented in support of the utility of the described compounds exclusively concerned compounds carrying an interacting substitution at the 5-position of the pyrimidine, in particular a bromovinyl substitution. In the absence of further support for the therapeutic activity of the compounds described in document D36 there were serious doubts that the phosphoramidate nucleosides lacking the substitution at the 5-position of the pyrimidine for interaction with an endogenous enzyme exhibited any anti-hyperproliferative activity. It was therefore on the basis of document D36 not credible that such compounds would actually be useful in the treatment or prevention of cancer.

The compounds of claim 1 of the main request did not carry a relevant substitution for interaction with an endogenous enzyme. This was particularly evident for the compounds in which Z represented hydrogen. Accordingly, these compounds were in view

of the information in document D36 not obvious as solution to the problem of providing alternative compounds for the treatment or prevention of cancer and thus involved an inventive step.

The arguments in support of an inventive step of the subject-matter of the main request also applied to the more narrowly defined subject-matter of the subsequent auxiliary requests.

(b) Auxiliary request 4 - amendments

The amendments in claim 1 of auxiliary request 4 with respect to claim 1 of the parent application included the restriction of the meaning of Y to "F" in combination with the deletion of "H" from the meaning of X.

These amendments to the meanings of Y and X represented a mere limitation of the scope of protection without generating another invention. They involved the shrinking of the list of options for the substitutions Y and X leaving a generic definition which was merely reduced in size without singling out a particular combination of meanings which had not been originally disclosed. In line with the considerations in T 615/95, T 859/94, T 50/97 and T 783/09, which were representative for the established jurisprudence, such an amendment involving the mere shrinking of lists of options, which maintains generic lists of alternative definitions differing from the original lists only by their smaller size without singling out a combination of features, was not objectionable.

Following G 2/10 the notion of a "technical contribution" as referred to in G 1/93, T 948/02 and G 1/03 was not to be understood as a modification to the established ("gold") standard for the assessment of amendments, according to which amendments can only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the application as filed. As confirmed in T 1937/17 the aspect of a "technical contribution" was not to be taken into account when assessing an amendment for compliance with Articles 76(1) and 123(2) EPC. However, even if the notion of a "technical contribution" as applied in T 948/02 were to be taken into account, it was evident that the amendments in auxiliary request 4 did not provide such a technical contribution, because the amendments merely removed the overlap with the definition of compounds from document D36 without giving rise to additional improvements or effects for which the application as filed provided no basis.

The same arguments applied with respect to the subject-matter of the subsequent auxiliary requests which included the same limitation in the meaning of X and Y in the definition of the claimed subject-matter as claim 1 of auxiliary request 4.

VIII. The arguments of the appellant-opponent relevant to the present decision are summarized as follows:

(a) Main request - inventive step

Document D36 represented the closest prior art. Within document D36 the compound of claim 12, which concerned a phosphoramidate carrying a benzyl-ester group, represented the most suitable starting point with respect to the exemplified compounds of claim 1 of the main request for which the patent presented experimental results, because these exemplified compounds also concerned phosphoramidates with a benzyl-ester group.

The differences between the compounds of claim 1 of the main request and the compound of claim 12 of document D36 concerned the presence of a substitution at the 2-position of the sugar moiety (X/Y) and partly a substitution at the 5-position of the pyrimidine moiety. From the experimental data reported in the patent it was evident that the compounds of claim 1 did not generally provide for an advantage over the prior art. The late filed submission by the appellant-patent proprietor regarding the prevention of cancer on the basis of the activity of the claimed compounds against HCV infection was not to be admitted into the appeal proceedings.

The objective technical problem was therefore the provision of mere alternative compounds with respect to the compounds of document D36.

Document D36 described phosphoramidate nucleosides of a general formula which overlapped with the

definition of compounds in claim 1 of the main request and presented the credible teaching that such compounds were useful in the treatment of a variety of pathologies involving hyperproliferative cells, including in the treatment of cancer.

No serious doubts regarding the teaching of document D36 with respect to the therapeutic utility of the compounds within overlap could be based on the explanations in document D36 regarding "ECTA"-compounds comprising a 5-substituted pyrimidine moiety, which only concerned one aspect of the teaching in document D36. Moreover, the patent itself provided no basis for concluding any utility of the compounds within the overlap, which had not already been disclosed in document D36.

Accordingly, document D36 suggested by itself that the compounds within the overlap of the definitions of compounds in document D36 and claim 1 of the main request, including pyrimidine derivatives having an alkyl group or hydrogen at the 5-position of the pyrimidine moiety, represented useful alternative agents for treatment of cancer.

The subject-matter of claim 1 of the main request therefore lacked an inventive step.

The same objection applied with respect to the subsequent auxiliary requests which included definitions of compounds overlapping with the definition of compounds in document D36.

(b) Auxiliary request 4 - amendments

The amendment in the definition of the compounds in claim 1 of auxiliary request 4 with respect to the definition of compounds in the parent application as filed included the limitation of the variable Y to the single meaning of F together with the deletion of the meaning of H from the list of options for X.

This amendment involving restrictions of multiple lists of variables resulted in the selection of a subgroup of compounds characterized by the dual substitution at the 2-position of the sugar moiety involving at least one fluoro-substitution. The parent application as filed presented no pointer towards the selection of this subgroup.

In line with the established jurisprudence represented by T 948/02 and T 801/02 the restricted subject-matter could not be considered as adequately based on the parent application merely because it still defined a generic group of compounds.

The multiple restrictions in claim 1 of auxiliary request 4 thus generated a subgroup of compounds which could not be directly and unambiguously derived from content of the parent application as filed.

IX. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of its main request filed as auxiliary request 1 with its statement of grounds of appeal.

Subsidiarily, the appellant-patent proprietor requested that the patent be maintained on the basis of auxiliary request 1-19 filed as auxiliary requests 2-20 with its statement of grounds of appeal or on the basis of one of auxiliary requests 20-107 filed as auxiliary requests 21-108 with its reply to the appeal filed by the opponent.

X. The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The appellant-opponent further requested that an amendment to the appellant-patent proprietor's case, namely the formulation of the objective technical problem as the provision of compounds useful in the treatment or prevention of cancer having regard to the HCV inhibiting activity of the compounds, not be admitted.

Reasons for the Decision

1. Admittance of submissions

In its communication under Article 15(1) RPBA (see section 2.3.4) the Board explained that it was of the preliminary opinion that the submission by the appellant-patent proprietor, that compounds such as sofosbuvir prevent hepatocellular carcinoma as a result of their efficacy in treatment of HCV infection and thereby present a solution to the problem of preventing cancer, was not to be admitted into the appeal proceedings in view of Articles 12(4) and 12(6) RPBA.

This submission represented in the Board's preliminary opinion an amendment to the appellant-patent proprietor's case with respect to the proceedings before the opposition division. The Board indicated that it was not convinced that this amendment was justified considering that the addressed objection regarding the suitability of sofosbuvir as anti-cancer agent had already been raised in the notice of opposition (see pages 44-46, sections 6.20-6.23). Moreover, the Board indicated that it was not convinced that the technical effect of prevention of hepatocellular carcinoma as a result of activity against HCV could be relied upon for the formulation of the problem to be solved, because the patent did not provide any pointer regarding this effect.

During the oral proceedings the appellant-patent proprietor relied with respect to this issue on its arguments presented in writing, which preceded the Board's communication.

The Board therefore confirmed its preliminary opinion and did not admit the submission concerning the prevention of cancer by compounds as claimed on the basis of their efficacy in treatment of HCV infection into the appeal proceedings in view of Articles 12(4) and 12(6) RPBA.

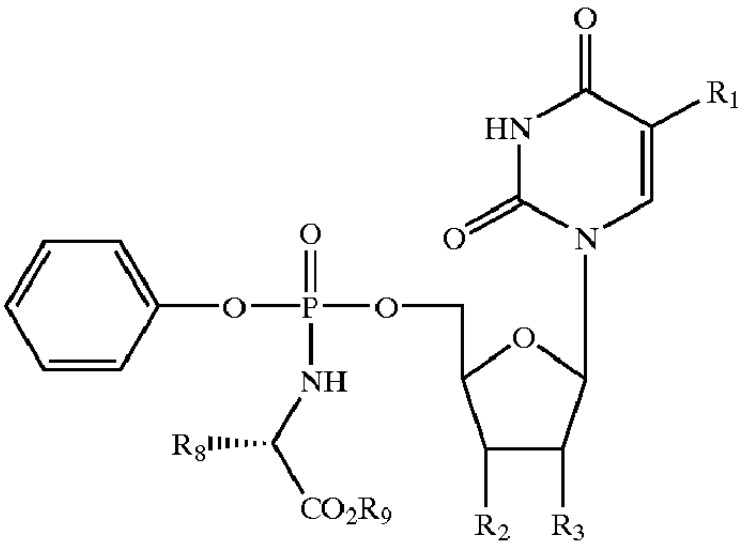
2. Main request (filed as auxiliary request 1 with the statement of grounds of appeal) - inventive step

2.1 Starting point in the prior art

The patent describes the defined compounds as useful in treatment and prophylaxis of cancer (see e.g. paragraphs [0001] and [0059]).

In support of this utility the patent (see pages 63-65, Table entries) reports the results from *in vitro* experiments indicating cytotoxicity of the tested compounds in terms of their EC50 values in a breast cancer cell line (MDA MB231), a human colon cancer cell line (HT115) and a human prostrate cancer cell line (PC-3). The tested compounds are nucleosides and phosphoramidates thereof carrying a substituted vinyl group at the 5-position of the pyrimidine moiety without further substitution at the 2-position of the sugar moiety (see Examples A and 1-95) as well as gemcitabine (see Example G), which are presented as comparative examples, and phosphoramidates of gemcitabine (see Examples 31, 40 and 41), which represent examples of the compounds of claim 1 of the main request in which X and Y are both F. In addition, the patent presents results from experiments in a mouse model involving xenografts of human cancer (colon HT115 and prostrate PC-3) indicating the effectiveness of Example 31 ("CPF31") in reducing tumour volume.

Document D36 describes phosphoramidate nucleosides of the general formula:



wherein R1 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, vinyl, propargyl and substituted derivatives thereof;
wherein R2 and R3 are independently the same or different and are selected from the group consisting of Br, Cl, F, I, H, OH, OC(=O)CH3 , -0-and -0-Rg, wherein Rg is a hydroxyl protecting group other than acetyl;
wherein R_8 is a side chain of any naturally occurring amino acid, its analogue or its isomer;
and wherein R9 is selected from the group consisting of hydrogen, an aliphatic group, an alicyclic group, an aromatic group, a heterocyclic group and an adamantly group and derivatives and analogs thereof.

Document D36 teaches that these compounds have utility in the treatment of hyperproliferative disease, including treatment of cancer (see D36, claims 1 and 29, see also paragraphs [0002], [0014]-[0017]). This teaching in document D36 is supported with experimental results for the exemplified compound NB1011 whose structure is shown in Table 2 of paragraph [0123]. NB1011 carries a bromovinyl group at the 5-position of the pyrimidine moiety and has no substitution at the 2-

position of the sugar moiety (compare R1 and R3 in the general formula). These results include cytotoxicity data for NB1011 in a variety of normal and tumor cell strains (see D36, paragraph [0374], Table 5).

As pointed out in the decision under appeal (see pages 33-35, section 5.2), document D36 thus describes compounds of a similar structure with a similar purpose as described in the patent for the compounds of claim 1 of the main request and therefore represents a suitable starting point in the prior art.

As further indicated in the decision under appeal (see page 35-36, section 5.4) and as argued by the appellant-opponent, the bromovinyl substituted benzyl-ester of the phosphoramidate nucleoside defined in claim 12 of document D36, which corresponds to the comparative example 2 ("CPF-2") described in the patent (see paragraph [0108]), represents a suitable reference point within document D36 with respect to the examples 31, 40 and 41 ("CPF-31", "CPF-40", and "CPF-41") of the patent, because these exemplified compounds are the benzyl-esters of related phosphoramidate nucleosides (see the patent paragraphs [0193], [0195] and [0197]).

2.2 Difference with the prior art

2.2.1 The difference between the compounds of claim 1 of the main request and the compound of claim 12 from document D36 concerns in the first place the substitution at the 2-position of the sugar moiety (X/F in the patent vs H/H in the compound of claim 12 in D36). This difference was not in dispute.

The compounds of claim 1 of the main request may further, at least partially, be distinguished from the

compound of claim 12 of document D36 in view of the substitution at the 5-position of the pyrimidine base. The compound from document D36 carries at this position a bromovinyl substitution whereas claim 1 of the main request defines at this position "Z", which is selected from the group H, alkyl and halogen.

2.3 Problem to be solved

As pointed out in the decision under appeal (see pages 36-37, section 5.5) the cytotoxicity in terms of the EC50 values reported in the patent (see page 63-65, Table entries) for Examples 31, 40 and 41 do not indicate any particular advantage for the compounds of claim 1 of the main request over comparative Example 2, which corresponds to the compound of claim 12 in document D36.

In the absence of evidence that the compounds defined in claim 1 of the main request are associated with an advantage over the closest prior art the Board concludes that starting from document D36 the problem to be solved could, at best, be seen in the provision of alternative agents with utility against cancer.

2.4 Assessment of the solution

2.4.1 The definition of compounds in claim 1 of the main request overlaps with the definition of the phosphoramidate nucleosides according to the general formula in document D36 (represented in section 2.1 above) when in the definition of claim 1 of the main request X represents H and Z represents H or alkyl.

In view of the teaching in document D36 that the phosphoramidate nucleosides according to the general

formula in D36 are useful in the treatment of hyperproliferative disease, including treatment of cancer, the skilled person would as a matter of obviousness expect that the compounds of claim 1 of the main request which fall within the overlap with the general formula of the phosphoramidate nucleosides in document D36 represent alternative agents with utility against cancer.

2.4.2 The appellant-patent proprietor argued that the utility of the compounds covered by the general formula in treating hyperproliferative disease as described in document D36 would not suggest that all of these compounds would be useful against cancer, because in accordance with document D36 the term hyperproliferative disease includes a variety of hyperproliferative diseases other than cancer.

The Board does not consider this argument convincing, because document D36 explicitly teaches the utility of the described compounds in the treatment of hyperproliferative disorders in general and mentions cancer as prominent example of such disorders (see D36, paragraphs [0014] to [0017]).

2.4.3 The appellant-patent proprietor further argued that the skilled person would have serious doubts as to the credibility of the teaching in document D36 regarding the utility of the compounds as broadly defined by the general formula in the treatment of hyperproliferative diseases in general, in particular in as far as the treatment of cancer is concerned.

As contended by the appellant-patent proprietor, document D36 indeed refers in its abstract and paragraphs [0013], [0016] and [0080] to 5-substituted

pyrimidine compounds ("5'-phosphoramidatyl, 1,**5**-substituted pyrimidine compounds") as the therapeutically active agents of its disclosure. However, in the same passages document D36 refers to "derivatives, analogs and pharmaceutically acceptable salts thereof". Moreover, in paragraph [0080] document D36 points out that the intended compounds are "nucleoside analogs comprising a substituted or unsubstituted uracil base covalently joined to a sugar modified by at least the addition of a 5'-phosphoramidate containing an amino acid residue." Accordingly, the teaching of document D36 regarding the therapeutic utility of the disclosed compounds is not limited to the 5-substituted pyrimidine compounds and the cited references to these 5-substituted pyrimidine compounds in document D36 do not contradict or cast doubt on the therapeutic utility of compounds of the general formula described in document D36.

As further argued by the appellant-patent proprietor, document D36 also mentions that the compounds carrying a substitution at the 5-position may interact with an endogenous intracellular enzyme such as thymidylate synthetase (TS) (see paragraphs [0080] and [0089]) and reports in this context that the tested compound NB1011 carrying a bromovinyl substitution at the 5-position acts as a TS ECTA compound (see paragraphs [0336] and [0341]). However, document D36 explicitly states that the interaction with an endogenous intracellular enzyme such as TS via a 5-substitution to the pyrimidine moiety only represents one aspect of the disclosure (see paragraphs [0015], [0046], [0080] and [0089]). The information in document D36 regarding a mechanism of action of the described 5-substituted pyrimidine compounds, including the tested compound NB1011, can therefore also not be considered to contradict or

otherwise cast doubt on the therapeutic utility of compounds of the general formula described in document D36.

At the same time the patent only provides experimental results for nucleosides carrying a substituted vinyl group at the 5-position of the pyrimidine moiety having no substitution at the 2-position of the sugar and nucleosides carrying a di-fluoro substitution at the 2-position of the sugar moiety, which do not fall within the overlap of the definition in claim 1 of the main request and the definition of the general formula in document D36. Accordingly, the patent itself provides no more concrete basis for assuming the relevant utility of these compounds than document D36.

The Board therefore considers that the arguments of the appellant-patent proprietor against the credibility of the teaching in document D36 regarding the therapeutic utility of the compounds covered by the described general formula, in particular the compounds within the overlap with the definition of compounds in claim 1 of the main request, remain speculative and are thus not convincing.

2.4.4 Accordingly, the Board concludes that the main request does not comply with the requirement of inventive step.

3. Auxiliary requests including H for X

Auxiliary requests 1-3, 10-13, 24-27, 34-37, 48-49, 52-53, 60-61, 64-65, 72-75, 84-87, 96-97 and 102-103 maintain the overlap in the definition of the compounds of formula I with the definition of the compounds by the general formula in document D36 due to the definition of X including H. The considerations

presented in section 2 above with respect to the main request therefore equally apply to these auxiliary requests.

Accordingly, the Board concludes that auxiliary requests 1-3, 10-13, 24-27, 34-37, 48-49, 52-53, 60-61, 64-65, 72-75, 84-87, 96-97 and 102-103 (filed as auxiliary requests 2-4, 11-14, 25-28, 35-38, 49-50, 53-54, 61-62, 65-66, 73-76, 85-88, 97-98 and 103-104) do not comply with the requirement of inventive step.

4. Auxiliary requests excluding H for X

4.1 Auxiliary request 4 (filed as auxiliary request 5)

4.1.1 The parent application as originally filed (see page 3, line 12 to page 4, line 14, see also claim 1) defined the variables X and Y for the compounds of formula I as follows:

"X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3)".

It was not in dispute that the amendments in accordance with claim 1 of auxiliary request 4 include with respect to the definition of the compounds of formula I in the parent application as filed the limitation of the meaning of Y to F in combination with the deletion of H from the list of options for X.

4.1.2 As confirmed in G 2/10 (see *inter alia* section 4.5.4), the assessment of amendments is to be based on what a skilled person would derive directly and unambiguously, using common general knowledge, from the (parent) application as originally filed (the "gold standard").

The Board observes that in accordance with the established jurisprudence regarding the deletion of meanings from multiple lists defining variables in a generic formula (see Case Law of the Boards of Appeal, 10th Edition, II.E.1.6.3 with reference to T 615/95, T 859/94, T 50/97, T 783/09, T 948/02 and T 801/02) it is not sufficient that the remaining subject-matter still relates to a generically defined group of compounds. In order to comply with Article 123(2) the deletion must not result in a particular combination of specific meanings which was not originally disclosed and which thereby generates another invention. In other words the amendment may not lead to a particular combination which is not derivable from the original application and is therefore potentially suitable to provide a technical contribution to the originally disclosed subject-matter as opposed to a mere restriction of the required protection which does not result in the definition of a new sub-class of compounds and is therefore not potentially suitable to provide a technical contribution to the original subject-matter.

4.1.3 In the patent as granted the definition of the compounds of formula I had already been limited with respect to the originally disclosed group of compounds by restriction of Y to a single meaning. Whilst such limitation is not objectionable as sole amendment, the combination of this limitation of Y with the further deletion of H in the meaning of X as defined in claim 1 of auxiliary request 4 singles out those compounds which are characterized by the combination of the features that the 2-position of the sugar moiety carries a dual substitution and that at least one of these substitutions is a fluoro-substitution. The Board considers this combination of features to define a

specific sub-group of compounds within the originally disclosed generic group of compounds, which is well suitable to provide for a technical contribution generating another invention.

The original disclosure does not provide any pointer to this sub-group of compounds. On the contrary, the parent application as filed (see page 9, line 16) explicitly includes in the defined preferred list of meanings for X and Y the option of H: "Preferably, X and Y are, independently, selected from the group consisting of F, H and OH". These preferred meanings for X and Y are also reflected by the examples in the original disclosure, which relate to compounds in which X and Y represent either both H or both F.

4.1.4 The appellant-patent proprietor argued that no technical contribution was associated with the amendments in auxiliary request 4, which would merely remove the overlap with the definition of compounds from document D36 without giving rise to improvements or effects for which the original disclosure provided no basis.

The appellant-patent proprietor does thereby not address the suitability of the sub-group of compounds resulting from the amendments to provide for a technical contribution that was not embodied by the originally described generic group of compounds, which to a substantial extent overlapped with the teaching in document D36.

4.1.5 The appellant-patent proprietor further argued with reference to G 2/10 and T 1937/17 that the notion of a technical contribution should actually not be taken into account at all.

The Board notes that in G 2/10 (see section 4.3) the Enlarged Board of Appeal explained that the notion of a "technical contribution", as referred to in G 1/93 (see section 16) in the context of conflicting requirements under Article 123(2) and (3) EPC and in G 1/03 (see sections 2.6 and 4) in the context of disclaimers for undisclosed subject-matter, was not intended to modify the "gold standard" for the assessment of amendments.

The Board agrees with the considerations in T 1937/17 (see sections 4.3 and 4.3.1) that, accordingly, in the context of an amendment which is found to be allowable or not allowable under the "gold standard" any investigation as to the potential for a technical contribution is without relevance.

However, amendments by the deletion of options from multiple lists of separate characteristics inherently include an aspect of combination and potentially involve an aspect of arbitrariness, which may complicate the assessment of whether such amendments remain within the limits of what the skilled person would directly and unambiguously derive from the original disclosure.

Following the explicit reference in G 2/10 to the applicability of the existing jurisprudence regarding the singling out of compounds or sub-classes of compounds or other so-called intermediate generalisations not specifically mentioned nor implicitly disclosed in the application as filed (see G 2/10, section 4.5.4), the Board understands in this context the notion of

"the remaining generic group of compounds differing from the original group only by its smaller size" *versus* "singling out an hitherto not specifically mentioned sub-class of compounds"

and the notion of

"mere restriction of the required protection" *versus* "generating another invention" or "suitable to provide a technical contribution to the originally disclosed subject-matter"

as developed in the jurisprudence (see in section Case Law of the Boards of Appeal, *supra*, section II.E.1.6.3) not as modifications of the "gold standard" for the assessment of amendments in the form of additional or alternative criteria, but rather as considerations which may arise from the application of this standard when assessing amendments by deletion of options from multiple lists and which may affirm the result of such assessment.

Accordingly, the Board considers that the observation that the deletion of options for X and Y in accordance with claim 1 of auxiliary request 4 is suitable to provide a technical contribution to the originally disclosed subject-matter supports the assessment that this amendment is not in compliance with the "gold standard".

4.1.6 The Board therefore concludes that auxiliary requests 4 does not comply with the requirement of Article 76(1) EPC.

4.2 The claims according to auxiliary requests 5-9, 14-23, 28-33, 38-47, 50-51, 54-59, 62-63, 66-71, 76-83, 88-95,

98-101 and 104-107 include the same limitation in the definition of X by the deletion of H as claim 1 of auxiliary request 4.

The same considerations as presented in section 4.1 above therefore apply with respect to these auxiliary requests.

Accordingly, the Board concludes that auxiliary requests 5-9, 14-23, 28-33, 38-47, 50-51, 54-59, 62-63, 66-71, 76-83, 88-95, 98-101 and 104-107 (filed as auxiliary requests 5-10, 15-24, 29-34, 39-48, 51-52, 55-60, 63-64, 67-72, 77-84, 89-96, 99-102 and 105-108) do not comply with the requirement of Article 76(1) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated