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D E C I S I O N
of 21 May 2003

Case Number: T 0682/99 - 3.3.1

Application Number: 91909127.2

Publication Number: 0527189

IPC: C07D 487/04

Language of the proceedings: EN

Title of invention:
Novel CC-1065 Analogs

Applicant:
PHARMACIA & UPJOHN COMPANY

Opponent:
-

Headword:
CC-1065 analogues/PHARMACIA

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and auxiliary requests 1 to 9 - inventive step (no) - obvious solution"

Decisions cited:
T 0020/81, T 0939/92, T 0249/88, T 1053/93

Catchword:
-

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Case Number: T 0682/99 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 21 May 2003

Appellant: PHARMACIA & UPJOHN COMPANY
301 Henrietta Street
Kalamazoo
Michigan 49001 (US)

Representative: Perry, Robert Edward
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 3 February 1999 refusing European patent application No. 91 909 127.2 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
J. P. B. Seitz

Summary of Facts and Submissions

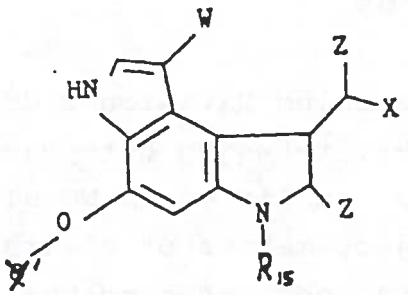
I. The appeal lies from the Examining Division's decision, dispatched on 3 February 1999, refusing European patent application No. 91 909 127.2, published as WO 91/16324, for the reason that the subject-matter of claims 1 to 29 underlying the decision was obvious over the cited prior art, such as document

(2) EP-A-0 154 445.

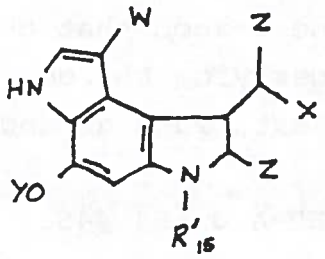
II. In particular, the Examining Division held that the claimed compounds differed from the known compounds by the presence of a group R_{50} comprising reactive moieties with which it is possible to form conjugates with eg monoclonal antibodies via reaction with substituent Y' of the compounds of formula IA or with substituent R'_{15} of the compounds of formulas IB. Since it was known that the radicals Y' or R'_{15} may considerably be modified without changing the antitumour activity qualitatively and since the idea of using tumour associated monoclonal antibody-conjugates in the treatment of tumours was known, the Examining Division was of the opinion that the claimed compounds were obviously derivable from the prior art.

III. With telefax dated 16 May 2003 the Appellant filed claims according to auxiliary requests 1 to 9 and at the oral proceedings before the Board, which took place on 21 May 2003, the Appellant filed a modified version of Claim 1 of the set of claims underlying the decision, so that the independent claims of the main request read as follows:

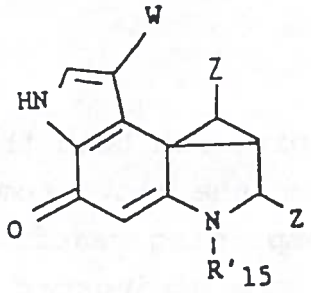
"1. A compound of Formula IA, IB or II:



IA



IB



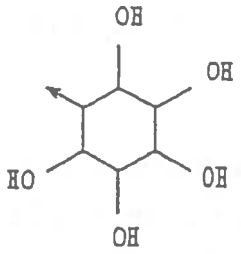
II

wherein W is selected from C_1-C_5 alkyl, phenyl or hydrogen;

wherein X is selected from azido, a halogen atom, cyanate, thiocyanate, isocyanate, thioisocyanate, phosphate diester (-PO(OR)$_2$), phosphonyl (-O-PO$_2$R), thiophosphonyl (-O-PSOR), sulfinyl (-O-SOR) or sulfonyl (-O-SO$_2$R);

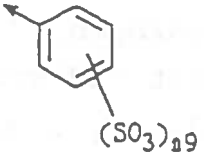
wherein Y is selected from hydrogen, -C(O)R, -C(S)R, -C(O)OR$_1$, S(O)$_2$R$_1$, -C(O)NR$_2$R$_3$, -C(S)NR$_2$R$_3$, -C(O)NHSO$_2$R$_4$, -C(O)CH$_2$(OCH$_2$CH$_2$)$_{n7}$O(C_1-C_3 alkyl) and $_{n7}$ is 0-5, or -C(O)(CH$_2$)$_{n8}$C(O)R$_b$ where $_{n8}$ is 0-10 and R$_b$ is selected from -OH (or a metal or amine salt thereof), -OR$_c$ where R$_c$ is -CH$_2$C(CH$_2$OH)$_3$ or R_{70}, and -N(R$_d$)R$_e$ where R$_d$ is hydrogen or C_1-C_4 alkyl, and R$_e$ is selected from -C(CH$_2$OH)$_3$, -CH$_2$C(CH$_2$OH)$_3$, -CH$_2$C(CH$_2$NH$_2$)$_3$, R_{70}, R_{71} or R_{72}

where R_{70} is



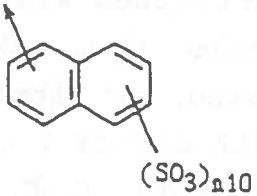
R_{70}

where R_{71} is



R_{71}

where R_{72} is



R_{72}

where n9 is 1 or 2 and n10 is 1-3;

wherein Y' is selected from $-C(O)R_{10}$, $-C(S)R_{10}$, $-C(O)OR_{10}$, $-S(O)_2R_{10}$, $-C(O)NR_{12}R_{13}$, $-C(S)NR_{12}R_{13}$, or $-C(O)NHSO_2R_{14}$;

wherein Z is selected from the group consisting of C_1-C_5 alkyl, phenyl or hydrogen;

wherein R is selected from the group consisting of C_1-C_{20} alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted

with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_1 is selected from C_1-C_{20} alkyl or phenyl optionally substituted with one, 2 of 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

wherein R_2 and R_3, being the same or different, are selected from hydrogen, C_1-C_{20} alkyl, or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; with the proviso that both R_2 and R_3 cannot be phenyl or substituted phenyl;

wherein R_4 is selected from C_1-C_{10} alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_{10}, R_{13} and R_{14}, being the same or different, are selected from -(C_1-C_{20} alkyl)$(CH_2)_nR_{50}$ or -(phenyl optionally substituted with one or two C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro)$(CH_2)_nR_{50}$;

wherein n is 0-10;

wherein R_{50} is selected from the group consisting of

(i) $-CO_2H$;

(ii) $-CH_2NH_2$;

(iii) -SH;

(iv) $-C(R_{60})(R_{61})$-SH wherein R_{60} and R_{61}, being the same or different, are C_1-C_4 alkyl or H;

(v) $-NHC(O)-(CH_2)_{n1}-C(R_{60})(R_{61})-SH$ wherein R_{60} and R_{61} are defined above and $_{n1}$ is 0-5;

(vi) $-C(O)NHNH_2$ (hydrazido);

(vii) $-NHNH_2$ (hydrazino);

(viii) $-CH_2OH$ (hydroxymethyl);

(ix) $-NHC(S)NH_2$ (thioureido);

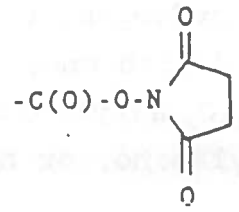
(x) $-CH_2NHC(O)NH_2$;

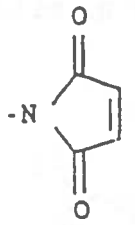
(xi) $-NHC(S)NHNH_2$;

(xii) $-C(O)CH_2X_1$ (X_1 is a halogen);

(xiii) $-CH_2X_1$ (halomethyl) wherein X_1 is a halogen;

(xiv) -CHO (aldehyde);

(xv)  (N-hydroxysuccimidyl);

(xvi)  (maleimide);

(xvii) $-C(R_{60})(R_{61})-C(O)NHNH_2$ wherein R_{60} and R_{61}, being the same or different, are C_1-C_4 alkyl or H;

(xviii) $-O(CH_2)_{n1}C(R_{60})(R_{61})-C(O)NHNH_2$ wherein R_{60}, R_{61}, and $_{n1}$ are defined above;

(xix) $-N(R_{62})(CH_2)_{n1}C(R_{60})(R_{61})C(O)NHNH_2$ wherein R_{60}, R_{61} and R_{62} are independently selected from C_1-C_4 alkyl or H and $_{n1}$ = 0-5;

(xx) $-O(CH2)_{n2}C(R_{60})(R_{61})C(O)NHNH_2$ ($_{n2}$= 1-5);

(xxi) $-NHR_{51}$;

(xxii) $-C(O)NHNHR_{51}$;

(xxiii) $-NHNHR_{51}$;

wherein R_{51} is an amine protecting group such as BOC (t-butoxycarbonyl), FMOC (9-fluorenylmethyloxycarbonyl), TFA (trifluoroacetate)amide), ALLOC (alloxycarbonyl), CBZ (benzoxycarbonyl), or TROC (trichloroethoxycarbonyl);

(xxiv) $-NHC(=NH)NH_2$ (guanadinyl); or

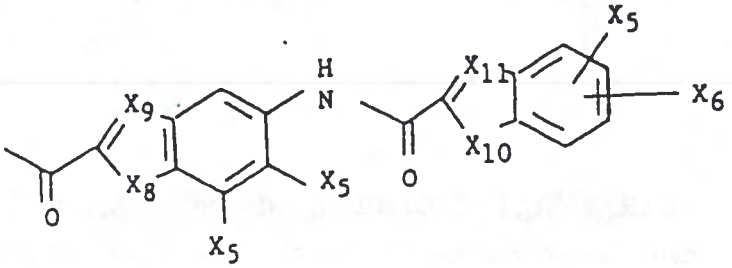
(xxv) $-B-M-(CH_2)_{n3}\ R_{52}$ wherein n_3 = 0-5; R_{52} is the same as R_{50} above (group (i)-(xxiv) only);

wherein B is an ester [-OC(O)- or -C(O)O-] or amide [-NHC(O)- or -C(O)NH-] bond;

wherein M is any compatible peptide or carbohydrate;
wherein R_{12} is selected from hydrogen, C_1-C_{20} alkyl, or phenyl optionally substituted with one, 2 of 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

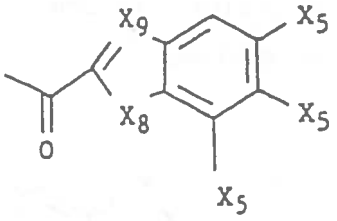
wherein R_{15} is a carbonylaryl group selected from the group consisting of

(a)



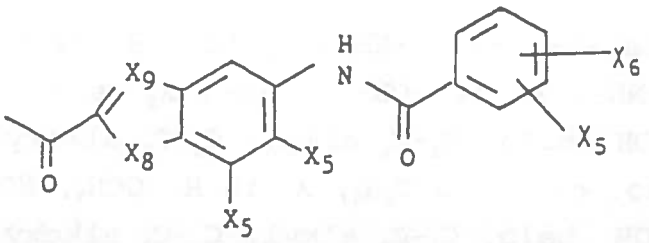
wherein X_8 is -O-, -S-, -NH-; X_9 is -CH- or N; X_{10} is -O-, -S-, -NH-; X_{11} is -CH- or -N-; X_5 may be the same or different and is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$; and X_6 is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$;

(b)



wherein X_5, X_8, X_9 have the meanings defined above;

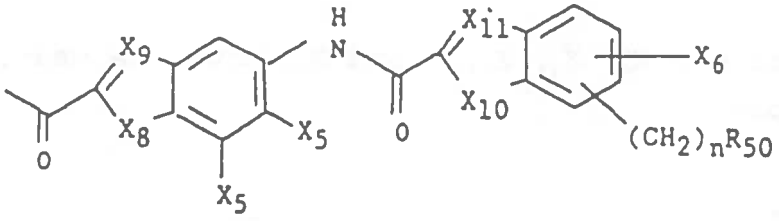
(c)



wherein X_5, X_6, X_8, X_9 have the meanings defined above;

wherein R'_{15} is a carbonylaryl group selected from the group consisting of

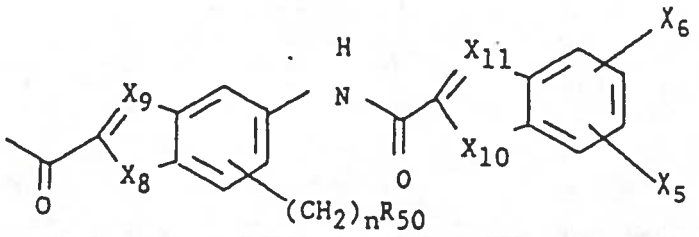
(d)



wherein $_8$ is -O-, -S-, -NH-; X_9 is -CH- or N; X_{10} is -O-, -S-, -NH-; X_{11} is -CH- or -N-; X_5 is the same or different and is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$; X_6

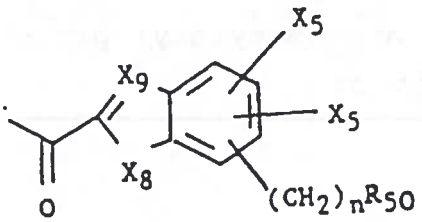
is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$; n and R_{50} have the meanings defined above;

(e)



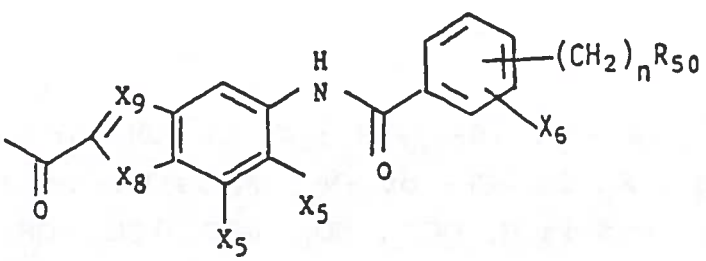
wherein X_8 is -O-, -S-, -NH-; X_9 is -CH- or N; X_{10} is -O-, -S-, -NH-; X_{11} is -CH- or -N-; X_5 is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$; X_6 is H, OCH_3, NO_2, $NHC(O)CH_3$, OH, halo, C_1-C_4 alkyl, C_1-C_3 alkoxy, C_2-C_6 dialkylamino, or $NHC(O)C_6H_5$; n and R_{50} have the meanings defined above;

(f)



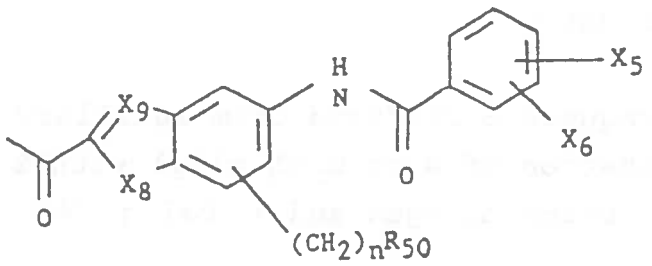
wherein X_5, X_8, X_9, n and R_{50} have the meanings defined above;

(g)



wherein X_5, X_6, X_8, X_9, n and R_{50} have the meanings defined above;

(h)



wherein X_5, X_6, X_8, X_9 n and R_{50} have the meanings defined above."

"28. A conjugate obtainable by linking a compound of any of claims 1 to 27, via reaction with a group R_{50}, with a monoclonal antibody."

"29. A conjugate obtainable by linking a compound of any of claims 1 to 27, via reaction with a group R_{50}, with a soluble human CD4 or a soluble human CD4 fragment capable of binding to the gp120 envelope portion of the human immuno-virus."

Auxiliary request 1 differed from the main request by limiting Claim 1 to compounds of formula IA having as R_{15} a group of formula (a) and compounds of formula IB having as R'_{15} a group of formula (d);

Auxiliary request 2 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl;

Auxiliary request 3 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl with Z being hydrogen;

Auxiliary request 4 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl with Z being hydrogen and X being halogen;

Auxiliary request 5 differed from auxiliary request 1 by X_8 being -NH-;

Auxiliary request 6 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl with Z being hydrogen, X being halogen and X_8 being -NH-;

Auxiliary request 7 differed from auxiliary request 1 by X_9 being -CH-;

Auxiliary request 8 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl with Z being hydrogen, X being halogen and X_9 being -CH-; and

Auxiliary request 9 differed from auxiliary request 1 by the limitation of W to C_1-C_5 alkyl with Z being hydrogen, X being halogen, X_8 being -NH- and X_9 being -CH-.

IV. The Appellant accepted that document (2) could qualify as the closest state of the art and that starting from document (2) the problem to be solved was to provide antitumour agents which can be selectively delivered to those target cells expressing the target antigen. Furthermore, the Appellant argued that the linker groups in the CC-1065 analogues must be selected in such a way that the CC-1065 analogues themselves maintain their activity in the free form and that they have desirable activity in the conjugated form. Since document (2) concerns CC-1065 analogues in their free form only and only the general concept of covalent attachment of substrate-linkers to monoclonal antibodies was known, for example, from document

(4) EP-A-0 088 695,

which was cited in the patent application, the incorporation of a group R_{50} in specific sites of a compound of formula Ia, IB or II was not made obvious by the prior art.

V. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of either:

- the main request, containing Claim 1 filed during the oral proceedings at 21 May 2003; or

- on the basis of the claims filed with telefax dated 16 May 2003 as auxiliary requests 1 to 9.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC and novelty*

Since the Board came to the conclusion that neither the main request nor any of the auxiliary requests meets the requirement of inventive step, it is superfluous to give any reasoning as to whether the requirements of Article 123(2) EPC and of novelty are met.

3. *Inventive step*

3.1 Main request

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light

thereof the technical problem which the invention addresses and solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

3.1.1 It was not contested that document (2) describes compounds having antitumour activity, which compounds differ from the claimed ones only by the nature of substituent R'_{15} in compounds of formula IB.

Document (2) discloses, namely, CC-1065 analogues according to present formula IB with Y being hydrogen and R'_{15} being a carbonylaryl group (d), wherein X_8 and X_{10} are each -NH-, X_9 and X_{11} are each -CH- and X_6 is H (see, in particular, formula II in combination with the definition of R_1 in lines 1 to 3 of page 2 and the carbonyl acyl group (ix) on page 6). Such CC-1065 analogues differ from the claimed ones only by the presence in the terminal bicyclic aromatic group of a substituent selected from H, OH, OCH_3, NO_2, NH_2, $NHC(O)CH_3$, $NHC(O)NH_2$, $NHCH_2C_6H_5$ or NH-CN instead of a group $(CH_2)_nR_{50}$.

3.1.2 From page 2, lines 20 to 31, of the published patent application it follows that it is the object of the invention to provide compounds, which have antitumour activity and which can be linked to monoclonal antibodies, either directly or via known linking groups, for selectively delivering the CC-1065 analogues to those target cells expressing the target antigen and thus selectively eliminating those diseased cells from the animal or human. Moreover, in the cited passage it is stated that those compounds can be linked to soluble human CD4 or soluble human CD4 protein fragment capable of binding to the gp 120 envelope protein of the human immuno-virus and thus eliminate virally infected cells.

The application in suit claims to solve these problems by the compounds defined in Claim 1 (see point III above).

3.1.3 The first point to be considered in assessing inventive step is then whether it has been convincingly shown that the problem underlying the patent application has effectively been solved by the compounds according to Claim 1.

3.1.4 As far as the property is concerned that the claimed compounds can be linked to soluble CD4 or a soluble human CD4 protein fragment capable of binding to the gp120 envelope protein of the human immuno-virus and thus eliminate virally infected cells, in the absence of any demonstration of such activity, it has not been rendered plausible that the alleged activity is effectively obtained with conjugates prepared from any of the claimed compounds.

It has been a generally accepted and established legal principle that a patent monopoly should be justified by the technical contribution to the art (see decision T 939/92 OJ EPO 1993, 309) and that unsupported advantages cannot be taken into consideration when determining the underlying problem (see T 20/81, OJ EPO 1982, 217). Since no technical contribution has been credibly established, the compounds according to Claim 1 cannot be considered to derive any inventive merit from such alleged unproven activity.

3.1.5 As far as the antitumour activity of the claimed compounds themselves is concerned, the data in Table I on page 94 of the application as filed only concern the antitumour activity of claimed compounds. In the absence of any comparison with known compounds, such

data are only useful for showing that claimed compounds have antitumour activity, but not that they have a superior effect.

Therefore, the question arises whether it would be unexpected that the claimed compounds have any antitumour activity.

From the data presented, inter alia, on pages 40 to 42 in document (2) it clearly follows that, although the antitumour activity of CC-1065 analogues is influenced by varying the substituents, some antitumour activity remains as long as the compounds contain the benzo[1,2-b;4,3-b']dipyrrol skeleton, as presented in formal B on page 47 of document (2). Therefore, as the presently claimed compounds as well as the compounds disclosed in document (2) contain that benzo[1,2-b;4,3-b']dipyrrol skeleton, there is no basis for considering that the claimed compounds would not have any antitumour activity.

Consequently, the compounds according to Claim 1 could be themselves expected to have antitumour activity, just as those known from document (2). This was never contested by the Appellant.

3.1.6 As far as the further property is concerned that the claimed compounds can be linked to monoclonal antibodies either directly or via known linking groups, as a means of selectively delivering the CC-1065 analogues to those target cells expressing the target antigen and thus selectively eliminating those diseased cells from the animal or human, document (2) also qualifies as the closest state of the art.

Starting from the disclosure of document (2) the problem to be solved is the provision of CC-1605 analogues allowing the selective delivery of the CC-1605 analogues to targeted cells expressing the target antigen.

It has never been contested that with the data provided by the Appellant with letter of 20 January 1994 an antitumour activity has been shown. Whether those data are suitable for rendering it plausible that such antitumour activity is obtained with conjugates of all claimed compounds is not relevant in the present case, since the Board comes to the conclusion for the following reasons that a skilled person would have expected antitumour activity of conjugates with compounds in accordance with the application in suit.

When trying to solve the stated problem, a skilled person starting from document (2) and looking for compounds allowing their selective delivery to targeted cells expressing a target antigen receives from document (4) information **how** such compounds could be linked to an antibody molecule and **which substituents** are useful in order to join such compound to a linker group attached to an antibody molecule, and that independently of the rest of the structure. Indeed, document (4) discloses the covalent attachment of a substrate-linker to monoclonal antibodies so that the resulting antibody conjugates retain the ability to bind antigen and activate complement, thus promoting the release of the compound in its active form at the target site (page 4, lines 13 to 18). The same linker groups for attachment to antibody molecules are described in Table III of document (4) as the ones described in Table III of the application. On page 34, lines 7 to 14, of document (4) it is taught that a compound may be joined to one end of the substrate

linker group and the other end of the linker group may be attached to a specific site on the antibody molecule. Furthermore, it is taught there that, if a compound has, for example, an amino group, the compound may be attached to the carboxy terminus of a peptide, amino acid or other suitably chosen linker via an amide bond. It also clearly follows from page 43, lines 3 to 17, of the published application that the coupling of compounds to antibodies by methods described in the literature cited there was well known in the art.

A skilled person would thus have expected that CC-1605 analogues containing an amine group in one of his substituents would be valuable candidates to be joined to one end of the linker group, the other end of the linker group being attached to a specific site on the antibody molecule, and that in such way the release of the compound in its active form at the target site could be promoted.

In this respect, the Appellant submitted, that it could not have been expected, that by linking an antibody to a CC-1605 analogue in the specific sites as defined in Claim 1, the release of a compound in its active form at the target site could be promoted.

However, when assessing inventive step it is not necessary to establish that the success of an envisaged solution of a technical problem was predictable with certainty. In order to render a solution obvious it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success (see decisions T 249/88, point 8 of the reasons, and T 1053/93, point 5.14 of the reasons).

In the present case, the skilled person receives from document (4) the clear information that, for example, amino groups enable the covalent attachment to an antibody molecule. Nothing was submitted by the Appellant from which the Board could reasonably conclude that the skilled person was deterred from following the teaching of the art. It was only necessary for him to confirm experimentally by routine methods that by incorporating, for example, an amine function into anyone of the substituents of a CC-1605 analogue the covalent attachment to an antibody molecule and the selective delivery to targeted cells was made possible.

3.1.7 Consequently, as the claimed compounds are obvious solutions to the problems underlying the application, Claim 1 and, thus, the main request, cannot be considered to meet the requirement of inventive step.

3.2 Auxiliary requests 1 to 9

Since compounds containing in one of their substituents, for example, an amine group are still embraced within the wording of Claim 1 of any of the auxiliary requests 1 to 9, none of the auxiliary requests can be considered to meet the requirement of inventive step for the reasons given in point 3.1 above.

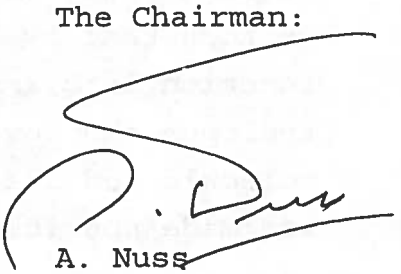
Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin



A. Nuss