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D E C I S I O N
of 29 June 2006

Case Number: T 1057/03 - 3.3.01

Application Number: 99941765.2

Publication Number: 1107969

IPC: C07D 487/04

Language of the proceedings: EN

Title of invention:
Collections of compounds

Applicant:
Spirogen Limited

Opponent:
-

Headword:
Collections/SPIROGEN

Relevant legal provisions:
EPC Art. 56, 84, 111(1)
EPC R. 68(2)

Keyword:
"Main and first auxiliary request: clarity (no)"
"Second auxiliary request: decision unreasoned - remittal to first instance"

Decisions cited:
T 0022/82, T 0068/85, T 0238/88, T 0939/92

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1057/03 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 29 June 2006

Appellant: Spirogen Limited
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Ryde,
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(GB)

Representative: Watson, Robert James
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 3 February 2003 refusing European application No. 99941765.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
R. Menapace

Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision to refuse the application 99 941 765.2, since the claimed collections of compounds were considered not to be inventive over the disclosure of document

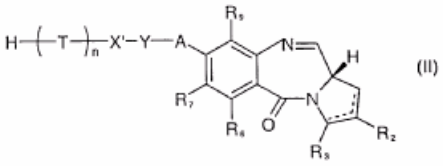
(4) J. Med. Chem. 1994, 37, pages 4529 to 4537.

In particular, the Examining Division was of the opinion that PBD (pyrrolobenzodiazepine) compounds were known from document (4) and that the introduction of a combinatorial unit and the attachment of those compounds to a solid support cannot be considered to represent an inventive concept. Moreover, the provision of a further library was considered *prima facie* obvious.

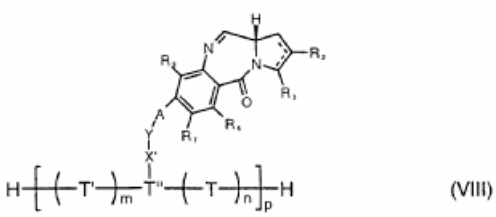
II. With letter of 16 May 2006 the Appellant filed sets of claims according to a main and six auxiliary requests.

III. Claim 1 according to the main request was concerned with a collection of compounds all of which are represented by either:

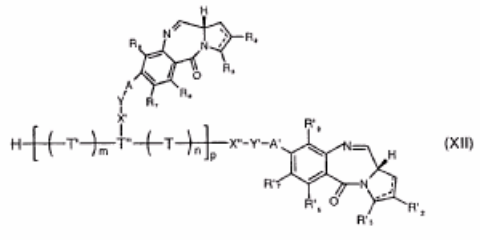
(1) formula II



(2) formula VIII



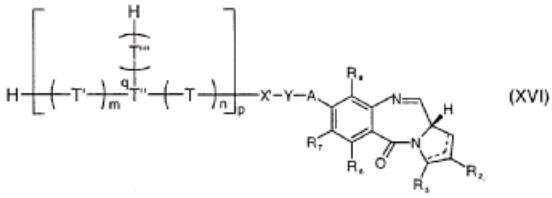
(3) formula XII



(XII)

or

(4) formula XVI



(XVI)

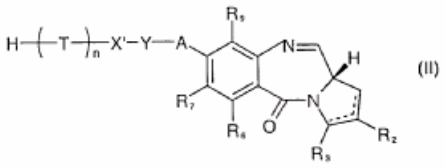
wherein *inter alia* T, T', T'' and T''' represent each a combinatorial unit.

Claim 1 according to the first auxiliary request was concerned with a collection of **at least 1000** compounds all of which are of formula (II), (VIII), (XII) or (XVI) as defined in Claim 1 of the main request.

The second auxiliary request consisted of 26 claims with the independent claims reading:

"1. A collection of compounds all of which are represented by either:

(1) formula II:



(II)

wherein:

A is O, S, NH, or a single bond;

R_2 and R_3 are independently selected from: H, R, OH, OR, =0, =CH-R, $=CH_2$, CH_2-CO_2R, CH_2-CO_2H, CH_2-SO_2R, O-SO_2R,

CO_2R, COR, CN and there is optionally a double bond between C1 and C2 or C2 and C3;

R_6, R_7, and R_9 are independently selected from H, R, OH, OR, halo, nitro, amino, Me_3Sn;
where R is an alkyl group having 1 to 10 carbon atoms, or an aralkyl group, of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups;

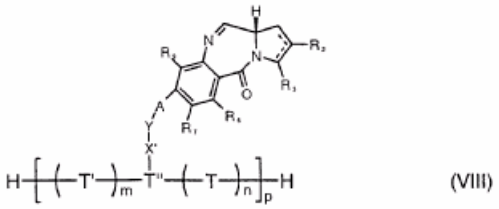
Y is a divalent group such that HY = R;

X' is CO, NH, S or O;

T is an amino acid residue; and

and n is a positive integer;

(2) formula VIII:



(VIII)

wherein X', Y, A, R_2, R_3, R_6, R_7, R_9, T are as defined above;

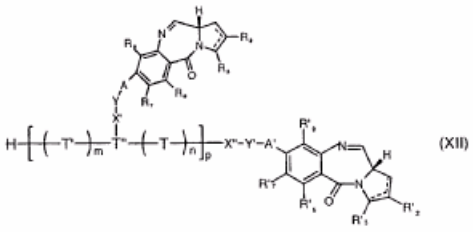
n and m are a positive integers, or one of them may be zero;

T' is an amino acid residue, where each T' may be different if m is greater than 1;

T'' is an amino acid residue which provides a site for the attachment of X'; and

p is a positive integer, where if p is greater than 1, for each repeating unit the meaning of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'' and values of n and m are independently selected;

(3) formula XII:

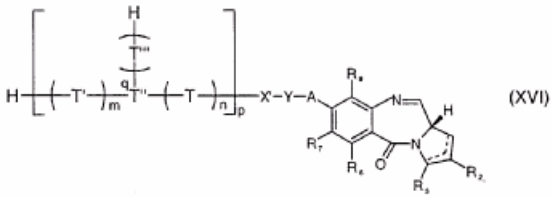


(XII)

wherein X', Y, A, R_7, R_2, R_3, R_6, R_9, T, T', T'', n, m and p are as defined above in part (2); and

X'', Y', A', R'_7, R'_2, R'_3, R'_6, R'_9 are selected from the same possibilities as X', Y, A, R_7, R_2, R_3, R_6, and R_9 respectively, and where if p is greater than 1, for each repeating unit the meanings of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', and T'' and the values of n and m may be independently selected; or

(4) formula XVI



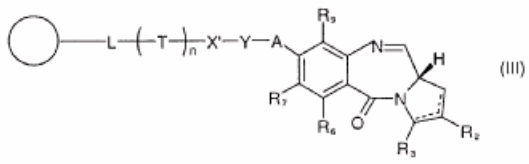
(XVI)

wherein X', Y, A, R_7, R_2, R_3, R_6, R_9, T, T', T'', n, m and p are as defined above in part (2); and

T''' and q are selected from the same possibilities as T and n respectively, and where if p is greater than 1, the meanings of T, T', T'' and T''' and values of n, m and q may be independently selected."

"12. A collection of compounds all of which are represented by either:

(1) formula III:



(III)

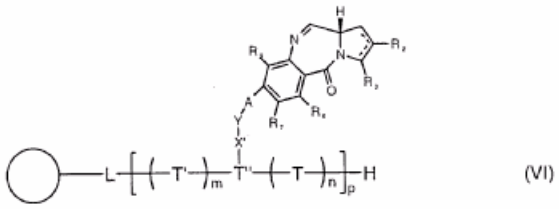
wherein

X', Y, A, R_7, R_2, R_3, R_6, R_9, T and n are as defined in any one of claims 1-11;

L is a linking group, or a single bond; and

○ is a solid support;

(2) formula VI:



(VI)

wherein ○, L, X', Y, A, R_2, R_3, R_6, R_7, R_9 and T are as defined above;

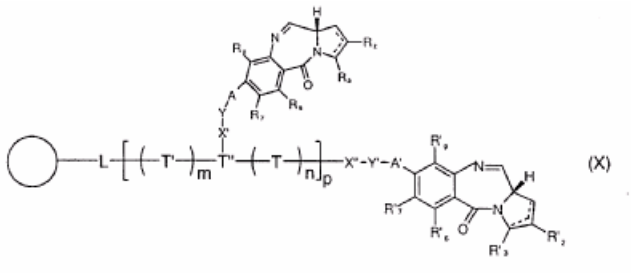
n and m are positive integers, or one of them may be zero;

T' is an amino acid residue, where each T' may be different if m is greater than 1;

T'' is an amino acid residue which provides a site for the attachment of X'; and

p is a positive integer, where if p is greater than 1, for each repeating unit, the meaning of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'' and the values of n and m are independently selected;

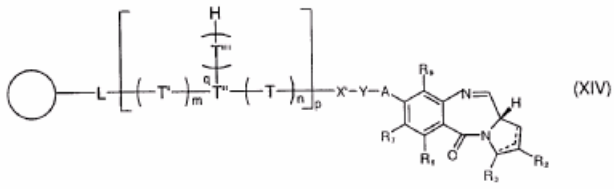
(3) formula X:



wherein O, L, X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', n, m and p are as defined in part (2); and

X'', Y', A', R'_2, R'_3, R'_6, R'_7 and R'_9 are selected from the same possibilities as X', Y, A, R_2, R_3, R_6, R_7 and R_9 respectively, and where if p is greater than 1, for each repeating unit the meaning of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'' and the values of n and m may be independently selected; or

(4) formula XIV:

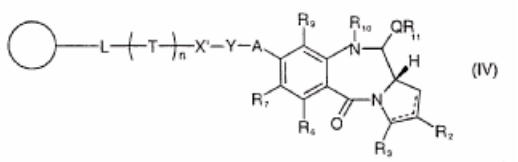


wherein O, L, X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', n, m and p are as defined above in part (2); and

T''' and q are selected from the same possibilities as T and n respectively; and where if p is greater than 1, for each repeating unit the meaning of T, T', T'', T''' and the values of n, m and q may be independently selected."

"13. A collection of compounds all of which are represented by either:

(1) formula IV:



(IV)

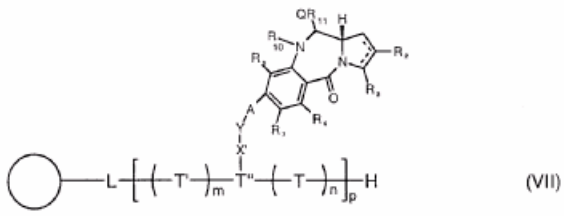
wherein X', Y, A, R_7, R_2, R_3, R_6, R_9, T, n, L and O are as defined in claim 12 for formula III;

R_{11} is either H or R;

Q is S, O or NH; and

R_{10} is a nitrogen protecting group;

(2) formula VII:

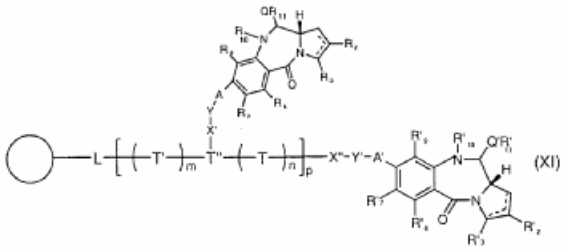


(VII)

wherein O, L, X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', n, m and p are as defined in claim 12 for formula VI; and

Q, R_{10}, and R_{11} are as defined above, and where if p is greater than 1, for each repeating unit the meanings of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', Q, R_{10}, R_{11} and the values of n and m are independently selected.

(3) formula XI



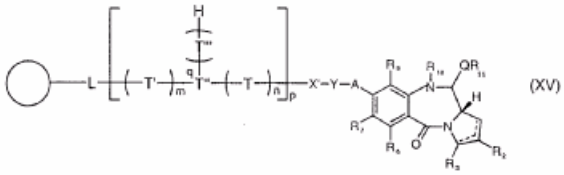
(XI)

wherein O, L, X', Y, A, R_2, R_3, R_6, R_7, R_9, X'', Y', A', R'_2, R'_3, R'_6, R'_7, R'_9, T, T', T'', n, m and p are as defined in claim 12 for formula X;

Q, R_{10}, and R_{11} are as defined above; and

Q', R'_{10}, and R'_{11}, have the same definitions as Q, R_{10}, R_{11} respectively, and where if p is greater than 1, for each repeating unit the meanings of X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', Q, R_{10}, R_{11} and the values of n and m are independently selected.

(4) A compound of formula XV:

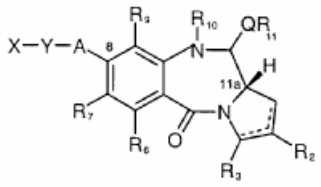


(XV)

wherein O, L, X', Y, A, R_2, R_3, R_6, R_7, R_9, T, T', T'', T''', n, m, p and q are as defined in claim 12 for formula XIV; and

Q, R_{10}, R_{11} are as defined above; and where if p is greater than 1, for each repeating unit the meanings of T, T', T'', T''' and the values of n, m and q may be independently selected."

"16. A compound of formula I:



(I)

wherein:

X is selected from COOH, NHZ, SH, or OH, where Z is either H or an amine protecting group;

A is O, S, NH or a single bond;

R_2 and R_3 are independently selected from: H, R, OH, OR, =O, =CH-R, $=CH_2$, CH_2-CO_2R, CH_2-CO_2H, CH_2-SO_2R, O-SO_2R, CO_2R, COR, CN and there is optionally a double bond between C1 and C2 or C2 and C3;

R_6, R_7, and R_9 are independently selected from H, R, OH, OR, halo, nitro, amino, Me_3Sn;

R_{11} is either H or R;

Q is S, O or NH;

R_{10} is a nitrogen protecting group;

where R is an alkyl group having 1 to 10 carbon atoms, or an aralkyl group, of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups; and

Y is a divalent group such that HY = R."

IV. Oral proceedings before the Board took place on 29 June 2006.

V. The Appellant essentially argued that the term "combinatorial unit", as presented in Claim 1 according to the main request and the first auxiliary request, is a generally accepted term in the art and, consequently, that the clarity of the claims is not affected thereby. Moreover, in favour of inventive step, the Appellant essentially argued that it was the objective of the claimed invention to reduce the time taken to identify a compound having a specific biological activity. Since it was the first time library technology had been applied to PBD compounds and since the claimed collections may be obtained by derivatising PBD compounds so that they can be attached to combinatorial units in such a way that

- the N10-C11 reactive site is protected,
- screening can still take place whilst the compounds are attached to solid support and

– growth of combinatorial chain can be carried out without interference from PBD moiety, removing problems of conflicting groups

the proposed solution was not obviously derivable from the prior art.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of one of the seven sets of claims filed as main and first to sixth auxiliary request by letter dated 16 May 2006.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request and first auxiliary request*

2.1 Article 84 EPC - Clarity

2.1.1 Article 84 EPC requires that the matter for which protection is sought be defined in the claims in a clear manner. Since Claim 1 in both sets of claims defines collections of compounds of formulas (II), (VIII), (XII) and (XVI), it must be unambiguously derivable from the wording of Claim 1, possibly in combination with the teaching of the description, which compounds may be comprised in the claimed collections and, therefore, all substituents in the compounds of formulas (II), (VIII), (XII) and (XVI) must be defined in an unambiguous way.

2.1.2 Whereas no objection arises against the clarity of the remaining substituents, the radicals T, T', T'' and T''', which are defined as a "combinatorial unit", cannot be considered to be defined in an unambiguous way.

Namely, in assessing whether the compounds of formula (II), (VIII), (XII) and (XVI) meet the requirement of clarity, it is decisive, whether a skilled person, considering the teaching in the description and his common general knowledge, would be able to find out which chemical radicals are to be understood as "a combinatorial unit" in T, T', T'' and T'''.

2.1.3 The only information about the meaning of the term "combinatorial unit" that can be found in the application is the one on page 17, line 15 to page 21, line 6. In this passage examples of suitable combinatorial units are provided and on page 17, lines 15 to 29, it is stated that a combinatorial unit is

> "any monomer unit which can be used to build a chain attached to the solid support, usually by a linking group. Examples of molecules suitable for such chain building are found in Schreiber et al. (JACS, 120, 1998, pp.23-29), which is incorporated herein by reference."

2.1.4 The Appellant submitted in the paragraph bridging pages 1 and 2 of the letter of 10 June 2003 that the combinatorial unit provides the necessary variation to allow the identification of compounds having highly specific biological activities and thus affects the

location at which the PBD moiety binds to DNA. As an explanation, the Appellant further submitted in the fourth paragraph on page 2 of the letter of 10 June 2003 that the combinatorial unit will lie adjacent the DNA strands, and by its interaction, will enable targeting of the PBD moiety to particular sequences.

However, since nowhere in the description any further information can be found about which monomer, useful to build a chain, may affect the location at which the PBD moiety binds to DNA, a skilled person cannot find out which compounds are embraced within the definition of Claim 1.

2.1.5 The Appellant further submitted that the article Schreiber et al. (see point 2.1.3) disclosed suitable molecules for such chain building and, thus, provided information to a skilled person which monomers could be useful as radical T, T', T'' and T'''.

The Board does not dispute that the Schreiber et al. article discloses monomers suitable for chain building. However, in deciding whether the term objected to in the claim is clear, it is not relevant whether a skilled person obtains information on monomers qualifying for chain building, but whether he could define which monomers are suitable as a "combinatorial unit" in the sense of the application in suit and which not. Such information is clearly missing in the Schreiber et al. article.

Moreover, the Appellant himself had to admit that the Schreiber et al. article is completely silent about the meaning of the term "combinatorial unit" and he did not

refer to any other document which could be considered as representing common general knowledge in the field concerned, wherefrom it could be deduced that chemical radicals are unambiguously defined by that term.

2.1.6 In arguing in favour of clarity, the Appellant referred to the principle set out in decision T 68/85 (OJ EPO 1987, 228), stating in essence that functional features defining a technical result are permissible, if such features cannot otherwise be defined more precisely and if these features provide instructions which are sufficiently clear for the skilled person to reduce them to practice. However, independent thereof whether the term "combinatorial unit" may be considered as a functional feature, for the reasons given above, it does not provide instructions which are sufficiently clear for a skilled person to reduce them to practice. Therefore the principle described in T 68/85 is not applicable in the present case.

2.1.7 In the absence of not only information in the description about which monomers are to be considered as combinatorial units and which not, but also any relevant common general knowledge thereupon, it is the position of the Board that a skilled person is not able to define in an unambiguous way which compound may be comprised in the claimed collections. Therefore, Claim 1 does not meet the requirement of clarity pursuant to Article 84 EPC.

2.2 Since, thus, the sets of claims according to the main and first auxiliary requests do not meet all requirements of the EPC, these requests are refused.

3. *Second auxiliary request*

3.1 Article 123(2) EPC

In comparison with the main and first auxiliary requests, the term "combinatorial unit" in the definition of T, T', T'' and T''' has been replaced by the term "amino acid residue".

The term "amino acid residue" is cited on page 17, lines 21 and 22, of the application as filed as an important example of a combinatorial unit.

Moreover, the remaining features of Claim 1 are a combination of the features of original Claims 1, 13, 22, 27, 31 and 33; the remaining features of Claim 12 are a combination of the features of original Claims 16, 20, 22, 25 and 29; the remaining features of Claim 13 are a combination of the features of original Claims 18, 22, 26, 30 and 33; and Claim 16 correspond with original Claim 1.

The requirement of Article 123(2) EPC is thus met.

3.2 Clarity

The Board does not have any reason to doubt that the term "amino acid residue" is a generally accepted term which unambiguously defines T, T', T'' and T''' and, thus, that the requirement of clarity is fulfilled.

Thus, the requirement of clarity is fulfilled.

3.3 Novelty

Since neither collections of PBD compounds (Claims 1, 12 and 13) nor PBD compounds as defined in Claim 16 were disclosed in any of the cited prior art documents, the requirement of novelty is fulfilled.

3.4 Inventive step

3.4.1 The Examining Division found that "[A]n inventive step cannot be attributed to the provision of a collection of compounds in analogy to the mere provision of new compounds which themselves do not have any unexpected effects (cf. decision T 22/82)" and that "[A]n inventive solution could only be ascribed to the collection if a specific (e.g. pharmaceutical) effect was shown.

However, the problem underlying the claimed invention is not the provision of compounds having unexpected effects, but rather the reduction of the time it takes to identify a compound having a specific biological activity (see point V above and page 1, line 22 ff. of the description).

Since T 22/82 (OJ EPO 1982, 341) is concerned with inventive step for a process for preparing **known** substances more economically and technologically more simply than in the prior art, which situation differs completely from the one in the present case, the principle described therein is not applicable in the present case.

Moreover, if the problem underlying the claimed invention is that stated above, an inventive step cannot be based on an unexpected effect of a particular compound. The claimed collections of compounds, proposed as a solution to the problem to be solved, are then rather intended to be used for screening the compounds comprised therein on a specific biological activity. Thus, in assessing inventive step, the relevant question seems to be rather whether it was obvious to provide the collections of compounds now claimed in order to speed up the process of identifying a compound having a specific biological activity in comparison with the classical method of synthesizing compounds one by one and separately testing each compound in a specific screening test. In this respect, in the contested decision also reference was made to decision the T 939/92 (OJ EPO 1996, 309). However, the principle described therein, namely that it must be made credible that substantially all claimed compounds possess the alleged activity, is not applicable in the present case, where the facts are significantly different as set out above.

3.4.2 The Applicant (now Appellant) extensively argued in the letter of 25 October 2002 that the solution offered by the present invention was obtained by applying library technology for the first time to PBD compounds and that the claimed collections may be obtained by derivatising PBD compounds so that they can be attached to combinatorial units in such a way that

- the N10-C11 reactive site is protected,
- screening can still take place whilst the compounds are attached to solid support and

– growth of combinatorial chain can be carried out without interference from PBD moiety, so removing problems of conflicting groups.

As not a single one of these steps was taught or suggested in the prior art, the claimed collections were not obviously derivable thereof.

Although the Applicant provided those arguments well before the oral proceedings before the Examining Division, namely 15 January 2003, there is not any trace in the contested decision showing these arguments of the Applicant.

3.4.3 Moreover, in the contested decision it is stated that "the preparation of libraries for the purpose of screening in order to identify chemical compounds with desired activities is considered to be within the routine work of a person skilled in the art."

Nowhere in the decision, however, can any explanation be found in respect of how the Examining Division had arrived at this conclusion, nor could the Board identify any support for it. Consequently, such statement is no more than an unsubstantiated allegation.

3.4.4 In order to comply with Rule 68(2) EPC, however, requiring that decisions before the EPO which are open to appeal shall be reasoned, the reasoning given in a decision open to appeal has to enable the Appellant and, in case of appeal, the Board of Appeal to examine whether the decision was justified or not. Therefore, a decision on inventive step has to contain the logical chain of reasoning used to justify the conclusion that

the claimed subject-matter does not involve an inventive step. As this is not the case for the presently contested decision refusing the application for the grant of a patent, the decision is in fact unreasoned and, therefore, contravenes the provisions of Rule 68(2) EPC.

4. The *de facto* absence of reasoning (see point 3.4.3) combined with the application of a wrong principle for assessing inventive step are also fundamental deficiencies pursuant Article 10 of the Rules of Procedure of the Boards of Appeal, which must have the consequence that the decision under appeal is to be set aside and the case is remitted to the first instance in application of Article 111(1) EPC for further prosecution on the basis of the second auxiliary request filed with letter of 16 May 2006.

4.1.1 For assessing inventive step when resuming the examination of the application in suit the well established problem-solution approach should be followed. Thereby 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 effectively solves** and

- to examine the obviousness of the claimed solution to this problem in view of the state of the art and common general knowledge, as reflected in "Combinatorial Chemistry", 1998 (N. K. Terrett)

edited by Oxford University Press and in some overview articles, such as, Angew. Chem. 1996, 108, pages 2436 to 2488.

4.1.2 Moreover, it should be verified whether dependent Claims 2 and 17 meet the requirement of Article 123(2) EPC. In particular, it is questionable whether support can be found in the application as filed, in particular, original Claim 2, for a lower alkyl group optionally substituted by one or more halo, hydroxy, amino or nitro groups.

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 for further prosecution on the basis of the second auxiliary request.

The Registrar: The Chairman:

N. Maslin A. Nuss