Dear Sirs,

Further to your communication of ............ concerning the European patent application number ...................... the following are my considerations on behalf of the applicant together with a duly amended set of claims.

The basis for the amendments

Claims 1 and 2: Table I and II respectively.

Claims 3 and 4: page 76, lines 8-18.

Claim 5: disclaimer from D II (see T 4/80 and T 433/86) for the meaning of R.

Claim 6: the meaning of R^III, page 76, lines 31-32.

Claim 10: Claim 6 as originally filed; the addition of a reference to pharmaceutically acceptable excipients or adjuvants is considered not to be in breach of Rule 88; as a matter of fact, when speaking of composition which can be used for the treatment for example of cancer (i.e. pharmaceutical composition), it is assumed that any skilled person would have derived directly and unambiguously that they also had to contain acceptable excipients or adjuvants (63/89); in particular, in example 1 a specific reference is made to aqueous solutions.

CLAIMS 1 AND 2

The compounds disclosed in Claims 1 and 2 are novel with respect to the state of the art and represent a selection invention with respect to the compounds generally disclosed in D I and D II.

In particular, although D I indicates that in the compounds of formula (A) and (B) R and R' might be aralkyl groups, a compound of the formula as claimed in Claims 1 and 2 (i.e. where R = benzyl) is never disclosed or exemplified.

On the contrary (see in particular the tables of page 82 of D I and those of page 84 of D II) other substituents are explicitly disclosed; thus, the selection made in Claims 1 and 2 is considered to be:

i) narrow;
ii) sufficiently far removed from the examples of the prior art;
iii) purposive, as the claimed compounds are those which are endowed with the stronger activity against leukaemia among all the exemplified compounds.

The compounds of Claims 1 and 2 are thus novel with respect of the state of the art (T 279/89).

Those compounds are also inventive. If the problem-solution approach is adopted in this case (C-IV, 9.5), the closest prior art might be considered either D I or D II.

D I discloses in fact compounds having a generical formula encompassing that of the claimed compounds. The D I compounds are, however, used as insecticidal.

D II, on the contrary, discloses compounds which do not encompass the claimed one but, however, are similar to them and can be used in the treatment of intestinal infections.
Irrespective of which of the two documents is considered the closest prior art in this case (if one!), the problem to be solved is that of providing compounds having a storing activity in the treatment of leukaemia.

Nowhere in these two cited documents is, however, suggested that the purposive selection made in Claims 1 and 2 would have lead to compounds having such a surprising activity.

These compounds are thus considered both novel and inventive and, consequently, *per se* patentable.

**CLAIMS 3 AND 4**

These two process claims are considered patentable as they lead to the production of novel and inventive compounds. (See C-IV, 9.5a and T 119/82).

**CLAIMS 5 AND 6**

Also in this case we are faced with a selection invention.

The compounds of Claims 5 and 6 are in fact already disclosed in D I where, however, only their use as insecticides is reported.

On the contrary, compounds similar to those of Claims 5-6 and endowed with therapeutical activity are generically disclosed in D II. Nevertheless, no compounds having the particular formula as claimed in Claims 5-6 are disclosed or exemplified in D II. D II makes in fact a generic reference to compounds where R is a hydrocarbon group having not more than 16 carbon atoms. The examples, however, only deal with compounds having from 6 to 16 carbon atoms, namely the preferred compounds indicated on page 83, line 20 of D II.

Consequently, following the claim form suggested in (C-IV, 4.2), Claims 5-6 are drafted in the typical form allowed for the *first therapeutical use of a directly known compound* (see also 65/83).

These claims are also inventive; the same reasoning as regards D I and D II made for Claims 1 and 2 applies also in this case.

In particular, if D I is considered to be the closest prior art, the man of the art would have found no indication or suggestion in such a document that compounds having insecticidal activity (i.e. kill insects) would have had a therapeutical activity with respect to other animals and would not have killed them as well.

Besides, the selection of compounds where R is a C₁-C₅ hydrocarbon group, is not suggested in D II as well which, on the contrary, would have lead the man of the art to eventually try to use compounds with larger hydrocarbon groups (n-heptyl, n-octyl, n-dodecyl ...).

**CLAIMS 8-9**

No explanation is considered necessary for these claims because they are dependent claims (C-IV, 9.5a).

**CLAIM 10**

The composition according to Claim 10 is considered novel and inventive as it contains novel and inventive compounds (those of Claims 1-2) or as it contains compounds which are novel and inventive as regards their first therapeutical use.
CLAIMS 11-14

These claims generically refer to the second (or first) therapeutical use of known or unknown compounds (those also fully within the scope of Claims 1-2).

Consequently, the wording suggested in C-IV, 4.2 and in 65/83 has been used.

The compounds falling within the wording of these claims are in fact already disclosed (and sometimes exemplified) in D I and/or D II.

Nowhere in these two documents is however indicated that these compounds could be used in the treatment of leukaemia or of cancer, irrespective of whether the problem-solution approach is used or not.

The killing of insects (D I) or the killing of the bacteria disclosed in D II are in fact considered to be technical problems completely different from the treatment of cancer and of leukaemia. Consequently, this second therapeutical use is considered to be novel and inventive.

The application is now in my opinion in order for grant.

If minor problems should arise, I would be happy if the Primary Examiner could eventually contact me by phone in order to speed up the grant procedure.

In any case, if the Examining Division intended to reject the application, oral proceedings are respectfully requested.

Sincerely yours.

CLAIMS

1. A compound of formula:
   C₆H₅-CH₂-NH-(CH₂)₃-NH-(CH₂)₄-NH-(CH₂)₃-CH₂₅-C₆H₅

2. A compound of formula:
   C₆H₅-CH₂-N-CH₂-N-(CH₂)₄-N-CH₂-N-CH₂₅-C₆H₅
      \ / \ /
     (CH₃)₃ (CH₃)₃

3. A process for the manufacture of a compound according to Claim 1 which comprises the steps of:
   a) replacing by protective groups all the hydrogen atoms of spermine which have to be hydrogen atoms in the desired product.
   b) reacting the so-obtained compound with a benzyl halide;
   c) replacing by hydrogen atoms the protective groups.

4. A process for the manufacture of a compound according to Claim 2 which comprises the step of condensing with formaldehyde a compound according to Claim 1.

5. A compound of formula:
   RHN-(CH₂)m-NH-(CH₂)n-NH-(CH₂)m-NHR
   wherein: m is an integer from 3 to 6
            n is an integer from 3 to 6
            and R is a C₁-C₅ alkyl group for use as a medicament.
6. A compound of formula:  
\[
R \quad R' \quad R
\quad R
\quad N-CH-N-(CH_2)_n-N-CH-N
\quad (CH_2)_m \quad (CH_2)_m
\]
wherein:  
m is an integer from 3 to 6  
n is an integer from 3 to 6  
R is a C_3-C_8 alkyl group  
and R' is H, a C_3-C_{12} alkyl group, an aryl or alkaryl group  
for use as a medicament.

7. A compound according to Claims 5-6  
wherein:  
m = 3 and n = 4.

8. a compound according to Claim 5  
wherein:  
R = n-pentyl, m = 3 and n = 4.

9. A compound according to Claim 6  
wherein:  
R' = H, R = ethyl, m = 3 and n = 4.

10. A pharmaceutical composition containing a compound according to Claims 1-2 or 5-9 together with  
pharmaceutically acceptable excipients and/or adjuvants.

11. Use of a compound of formula:  
\[
R'R-N-(CH_2)_n-N(R')-(CH_2)_n-N(R')-(CH_2)_m-NRR'
\]
wherein:  
m is an integer from 3 to 6  
n is an integer from 3 to 6  
and the groups R, R' and R'' may be the same or different and are, independently of one another,  
hydrogen atoms or C_3-C_{16} hydrocarbon groups, with the proviso that at least one of the R, R' and  
R'' groups is not hydrogen,  
for the manufacture of a medicament for the treatment of cancer or leukaemia.

12. Use of a compound according to Claim 11  
wherein:  
m = 3, n = 4, both R' and R'' groups are hydrogen atoms and R is selected from methyl,  
ethyl, propyl, butyl, n-pentyl, n-hexyl, n-octyl, n-decyl, aryl groups, alkaryl groups and  
aralkyl groups.

13. Use of a compound of formula:  
\[
R \quad R'^{\prime} \quad R
\quad R
\quad N-CH-N-(CH_2)_n-N-CH-N
\quad (CH_2)_m \quad (CH_2)_m
\]
wherein:  
m, n and R have the same meanings as in Claim 11  
and R' is a hydrogen atom, a C_3-C_{12} alkyl group, an aryl or an alkaryl group  
for the manufacture of a medicament for the treatment of cancer or leukaemia.

14. Use of a compound according to Claim 13  
wherein:  
m = 3, n = 4, R' = H and R has the same meaning as in Claim 12.