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21 September 1995 (21.09.95)

(54) Title: CALIXARENE-BASED COMPOUNDS HAVING ANTIBACTERIAL, ANTIFUNGAL, ANTICANCER-HIV ACTIVITY

(57) Abstract

Calixarene-based compounds are described which have biological activity, particularly anti-bacterial, anti-fungal, anti-cancer and anti-viral activity. Some compounds have been found to have anti-HIV activity. The compounds are calixarenes or oxacalixarenes, acylic phenyl-formaldehyde oligomers, cyclotriveratrylene derivatives, cyclic tetrameric resorcinol-aldehyde derivatives known as Hogberg compounds and cyclic tetrameric pyrogallol-aldehyde derivatives.

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INTERNATIONAL SEARCH REPORT

Interr. ial Application No
PCT/IE 95/00008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D313/00 C07D323/00 C07D321/00 A61K31/35 C07C69/712

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO,A,94 03164 (GENELABS TECH INC ;HWANG KOU M (US); QI YOU MAO (US); LIU SU YING) 17 February 1994 see ---	1-11,13, 15-17
X	WO,A,92 13542 (RHONE POULENC RORER SA) 20 August 1992 see ---	1,11,13, 15-17
X	WO,A,92 12709 (GENELABS INC) 6 August 1992 see ---	1-11,13, 15-17
X	US,A,4 604 404 (MUNSON JR HARRY R ET AL) 5 August 1986 see the whole document --- -/--	1-11,13, 15-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 June 1995	24. 08. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 210 216 (HARRIS STEPHEN J ET AL) 11 May 1993 see claim 1 ---	1-11,13, 15-17
X	EP,A,0 490 631 (HARRIS STEVEN J ;MCKERVEY MICHAEL ANTHONY (GB); SVEHLA GYULA (IE);) 17 June 1992 see claim 1 ---	1-11,13, 15-17
X	EP,A,0 432 990 (LOCTITE IRELAND LTD) 19 June 1991 see claim 1 ---	1-11,13, 15-17
X	EP,A,0 432 989 (LOCTITE IRELAND LTD) 19 June 1991 see claim 1 ---	1-11,13, 15-17
X	EP,A,0 309 291 (LOCTITE IRELAND LTD) 29 March 1989 cited in the application see claim 1 ---	1-11,13, 15-17
X	EP,A,0 279 521 (LOCTITE IRELAND LTD) 24 August 1988 see claim 1 ---	1-11,13, 15-17
X	EP,A,0 262 910 (LOCTITE IRELAND LTD) 6 April 1988 cited in the application see claim 1 ---	1-11,13, 15-17
X	EP,A,0 259 016 (LOCTITE IRELAND LTD) 9 March 1988 see claim 1 ---	1-11,13, 15-17
Y	ACC.CHEM.RES., vol.16, pages 161 - 170 GUTSCHE,C.D. 'Calixarenes' see ---	1-11,13, 15-17
Y	INT.J.CANCER, vol.7, 19 October 0 pages 34 - 49 CARTER,R.L. ET AL. 'Lysosomal changes and enhanced metastatic growth : an experimental study of the effects of some non-ionic surfactants' * see in particular page 36, formula II * ---	1-11,13, 15-17
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EUROP.J.CANCER, vol.7, 19 October 0 pages 533 - 544 FGRANCHI,G. ET AL. 'Triton WR 139 (TWR) , an inhibitor of Cancer Dissemination and Metastases' see -----	1-11,13, 15-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I national application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.
Claim 1 has been searched incompletely (formula I a, e)
Claim 12 has not been searched (open ended, unlimited)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please see attached sheet ./.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The closest prior with respect to the parts of the present application is to be found in :

(1) WO-A-92/13 542

(2) WO-A-92/12 709

(3) US-A-46 04 404

(4) US-A-52 10 216

(5) EP-A-0 490 631

(6) EP-A-0 432 990

(7) EP-A-0 432 989

(8) EP-A-0 309 291

(9) EP-A-0 279 521

(10) EP-A-0 262 910

(11) Acc.Chem.Res. 16, 161 (1983)

(12) Int.J.Cancer 7, 34 (1971)

(13) Europ.J.Cancer 7, 533 (1971)

The application-in-suit relates to compounds having biological activity, particularly (oxa-)calixarenes (see page 1, lines 1-3), having antibacterial, anti-fungal, anti-cancer

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

and anti-viral, particularly anti-HIV activity. On page 5, lines 30-32, it is said that at least some of the claimed derivatives possess metal ion complexing activity. Accordingly, the first (technical) problem underlying the application can be regarded as the provision of (oxa-)calixarene compounds with the above activities and/or effects.
The application lacks unity within the meaning of Rule 13 PCT since all inventions are not so linked as to form a single general inventive concept. The separate inventions/groups of inventions are:

1. Calixarene or Oxacalixarene-derivatives and their analogues (see formula I on page 6 and formula VI on page 9 and claims 1(a)+(e), 3, 5-11, 13, 15-17)

2. Cyclotrivatrylene derivatives and their analogues (see formula III on page 7 and claims 1(b), 3, 5-11, 13, 15-17)

3. Cyclic tetrameric resorcinol/pyrogallol-aldehyde derivatives and their analogues (see formula IV on page 8 and formula V on page 8 and claims 1(c)+(d), 3, 5-11, 13, 15-17)

4. Ayclic phenol-formaldehyde oligomers and their analogues (see formula II on page 7 and claims 2, 4 and 13)

These inventions are clearly distinct from each other and thus are not so linked as to form a single inventive concept within the meaning of Rule 13 (1) PCT for the following reasons:

1. Having regard to the available prior art, no common novel technical (structural) elements rendering each of the respective claimed subject-matter novel over the respective prior art could be identified, with the consequence that the claimed products per se do not possess a common technical

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

feature in order to belong to a common inventive concept in the sense of Rule 13 (1) PCT .
The requirements of a technical interrelationship and the same or corresponding special technical feature as defined in Rule 13 (2) PCT shall be considered to be met, when all alternatives are of a similar nature. Alternatives of chemical compounds are considered as being of similar nature if

a) all alternatives have a common property and

b) a common structure is present,i.e. a significant structural element is shared by all alternatives.

Requirement b) obviously is not met in the present case. Whether requirement a) is met cannot be decided at this stage of the procedure. Additionally, for the compounds of the first invention as described above no novel technical structural feature can be identified vis-a-vis the prior art (1) - (10) i.e. the formula (I) and (VI) overlap with those of the cited prior art documents.
In case a novel structural element could be identified, the problem underlying the first invention therefor could be seen in the provision of (oxa-)calixarene compounds having anti-bacterial, anti-fungal, anti-cancer and anti-viral, particularly anti-HIV activity. Since this concept is already known 'inter alia' from the prior art (1) - (3), (12) and (13) (compare e.g. the structure of Macrocyclon in (12)), even if this were a single general concept, it does not represent the single general inventive concept required according to Rule 13 (1) PCT. The relevant fact is that taking into account the available prior art (i.e. non-unity à posteriori), claims 1 and 2 do not allow the definition of a common technical / structural feature (a " special technical feature " in the sense of Rule 13 (2) PCT) which would display a technical relationship between all the inventions.
Additionally, since a preliminary search for the other inven-

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

tions did not reveal documents, from which the claimed derivatives could structurally or technically differ in a similar manner, the respective problem underlying the other inventions is to be considered the provision of cyclotrivatrylene derivatives, of cyclic tetrameric aldehyde derivatives and of ayclic phenol-formaldehyde oligomers each having antibacterial, anti-fungal, anti-cancer and anti-viral, particularly anti-HIV activity .
The respective (structural) novel elements are different in comparison with the prior art. The solution according to the alleged inventions consist in a series of families of compounds which as far as the first invention is concerned insofar as such structures are already known for the same activity (compare e.g. documents (1) - (3), (12) and (13)), represent pure alternatives (analogues) to the respective closest state of the art (first invention).

2. Even if all claimed families of compounds would illustrate a common structural element, this could only represent a single general concept, but it cannot represent the single general inventive concept required according to Rule 13 (1) PCT. The relevant fact in this particular case is that taking into account the available prior art (i.e. non-unity à posteriori), claims 1 and 2 do not allow the definition of a common technical (structural) feature (a " special technical feature " in the sense of Rule 13 (2) PCT) which would display a technical relationship between the inventions.

3. Moreover, the Search Examiner is of the opinion that the question of the technical and /or structural element rendering an invention novel is linked to the question of unity of the invention. The modifying feature should not only characterize the invention in the claim, i.e. distinguish it from the prior art, but must contribute causally to the improvement of the capability thereby achieved. Consequently, there can be only one novelty and one inventive step per application.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Having regard to the link between novelty and unity, it is indispensable that the Applicant comments on the common structural element which would unambiguously render the claimed subject-matter novel and unitary.

4. Since the above mentioned biological activity is already known from the prior art, it cannot serve as a special technical feature which would represent the contribution over the prior art as to form a general inventive concept. The same activity is already known for derivatives which are analogues of those described in the prior art i.e. this common concept is neither novel nor inventive. The requisite unity of invention therefore no longer exists inasmuch as the subject- matter of some of the (in)dependent claims, even when considering the description, is no longer linked with the subject-matter of any independent claims by a common inventive concept i.e. the solution of the above problem is not inventive.

5. Neither one the above cited structural features nor any corresponding technical feature is present in all the independent claims, so that the technical relationship between the subject-matter of the claims required by Rule 13 (1) PCT is lacking, and the requirement for unity of invention is not fulfilled.
There are/is no inventions/groups of inventions having a solution of their own, which would have something in common and a technical link could be seen between them, which could form an a common inventive concept and, thus would support the unity of the invention. Additionally it is noted that according to the description different methods for their synthesis of the compounds of the inventions 1 - 4 have to be applied.

6. In summary, it follows that the regulatory function of Rule 13 PCT is not taken into due account (prohibition of unjustified saving of fees and need for ready comprehensibility). It would be unfair to regard as having unity of inven-

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

tion those applications which, because of their heterogeneous content, entail a far greater than average expense in the procedure up to grant, especially in respect of search, since this expense must partly be born by the fees levied for other applications. Consequently, there is a lack of unity, and the different inventions not belonging to a single inventive concept are formulated as the different subjects in the communication pursuant to Article 34 (3) (a) PCT.

7. The search has been carried out on the basis of the first invention as described above. The Applicant may want to restrict the claims. If they were restricted to those dealing with any one of the above identified inventions/groups of inventions, they would then comply with the requirements of unity of invention. Alternatively, though a full preliminary search report has not been established, a full preliminary examination may be conducted, providing that additional preliminary examination fees are paid (Article 34 (3) (a), Rule 68 (2) PCT).

iii) Incomplete Search

1. Subject-matter excluded from patentability:

Claim 14 is directed to a method of treatment of human /animal body. Therefore a search could only be carried out based on the alleged effects of the compounds (Rule 39.IV PCT).

2. Obscurities, inconsistencies, contradictions:

2.1 Obscurities

Claim 12 is no dependant claim and in its unlimited form cannot be searched. Subject-matter identified by the term " preferably " in an independent claim should be made the subject of a dependent claim (Articles 5 and 6 PCT, clarity).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

2.2 Lack of conciseness, Incomplete Search:
Formula (i) and (VI) only contain a minor fixed part and display a large number of variables , which may also contain variables. Consequently, the scope of the claims cannot be evaluated and an exhaustive search is thus not possible. The search has been based on the explicitly claimed compounds for which n+m is 4.
Moreover, expressions like " hydrocarbyl, a substituted derivative thereof, part of a cyclic polyene antibiotic/ antifungal drug or part of a cyclic nitrogen heterocycle, is a similar residue " together with all the claimed possible combinations of the parameters in claims 1 and 2 and the dependant claims embrace such a number of conceivable structures (families of compounds), that a comprehensive and economically justified search is precluded. It is noted that the expressions " a substituted derivative thereof ", " part of a cyclic polyene antibiotic/ antifungal drug or part of a cyclic nitrogen heterocycle" and " is a similar residue " are speculative in the sense of Article 33 (3) PCT, embracing a great variety of structural possibilities not yet explored by the Applicant, the effect of which cannot be foreseen having regard to the problem underlying the present application. Moreover, such a definition creates unnecessary overlap and selection situations. E.g. such expressions encompasses any heterocycle - including any other moiety being known with the alleged activity. Furthermore, also the attachment of other biophoric/ pharmacophoric molecules as well as bioconjugates are embraced, so that the actual biological activity of e.g. the resulting hybrid molecules is unpredictable. Having regard to the problem underlying the present application it cannot be foreseen, whether such molecules are either an obvious solution or a solution to the problem at all.

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inten nal Application No
PCT/IE 95/00008

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